**Supplementary Content**

**eSearch strategy.** Search strategy for review question 1.

**eIncluded articles 1.** Studies/citations retained for review question 1 in the present systematic review

**eExclusion reasons 1.** Studies/citations discarded after assessing their full text for review question 1, with reasons for exclusions.

**eTable 1.** Summary of characteristics of included case-control/cross-sectional studies (*n* = 13)

**eFigure 1.** Caterpillar plot of pooled prevalence of overall headache in children with ADHD

**eFigure 2.** Funnel plot of epidemiological studies on the association between ADHD and headache among children

**eIncluded articles 2.** Studies/citations retained for review question 2 in the present meta-analysis

**eExclusion reasons 2.** Studies/citations discarded after assessing their full text for review question 2, with reasons for exclusions.

**eTable 2.** Summary of characteristics of included clinical trials (*n* = 58)

**eFigure 3.** Forest plot of risk of headache between amphetamine treatment groups and placebo groups

**eFigure 4.** Funnel plot of trials on the association between amphetamine and headache among children with ADHD

**eFigure 5.** Forest plot of risk of headache between atomoxetine treatment groups and placebo groups, with subgroup analysis based on maximum dosage

**eFigure 6.** Forest plot of risk of headache between atomoxetine treatment groups and placebo groups, with subgroup analysis based on dosing strategy

**eFigure 7.** Funnel plot of trials on the association between atomoxetine and headache among children with ADHD

**eFigure 8.** Forest plot of risk of headache between guanfacine treatment groups and placebo groups

**eFigure 9.** Funnel plot of trials on the association between guanfacine and headache among children with ADHD

**eFigure 10.** Forest plot of risk of headache between methylphenidate treatment groups and placebo groups

**eFigure 11.** Funnel plot of trials on the association between methylphenidate and headache among children with ADHD

**eFigure 12.** Forest plot of risk of headache between modafinil treatment groups and placebo groups

**eFigure 13.** Funnel plot of trials on the association between modafinil and headache among children with ADHD

**eFigure 14.** Caterpillar plot of trials on the prevalence of headache among children with ADHD treated with ADHD medications

**eFigure 15.** Caterpillar plot of trials on the prevalence of headache among children with ADHD in placebo arms

**eFigure 16.** Caterpillar plot of trials on the prevalence of headache among youths with ADHD in placebo arms based on different age groups

**eSearch strategy.** Search strategy for review question 1.

Documentation of search strategies

University Library search consultation group

Date: January 26, 2021

Topic/research question: Headache in ADHD: comorbidity and effects of medication

Name of researcher(s): Pei-Yin Pan, Ulf Jonsson & Sven Bölte, KBH/Center of Neurodevelopmental Disorders at Karolinska Institutet (KIND)

Librarian(s): Magdalena Svanberg, Emma-Lotta Säätelä & Narcisa Hannerz

Databases:

1. Medline (Ovid)
2. Embase (embase.com)
3. PsycInfo (Ovid)

Total number of hits:

* Before deduplication: 4,350
* After deduplication: 3,512

Comments:

1. Medline

|  |  |
| --- | --- |
| Interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily  Date of Search: 26 January 2021  Number of hits: 641  Comment: In Ovid, two or more words are automatically searched as phrases; i.e. no quotation marks are needed | Field labels   * exp/ = exploded MeSH term * / = non exploded MeSH term * .ti,ab,kf. = title, abstract and author keywords * adjx = within x words, regardless of order * \* = truncation of word for alternate endings |
| Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily**1946 to January 25, 2021 Search Strategy:   |  |  |  | | --- | --- | --- | | **#** | **Searches** | **Results** | | 1 | exp Attention Deficit Disorder with Hyperactivity/ | 29522 | | 2 | ((attention or hyperactiv\* or inattention) adj3 (deficit\* or disabilit\* or disorder\*)).ti,ab,kf. | 35204 | | 3 | (hyperactivity and (attention or inattention)).ti,ab,kf. | 29719 | | 4 | (addh or adhd or hyperkinetic\*).ti,ab,kf. | 30129 | | 5 | or/1-4 | 51180 | | 6 | Headache/ | 28194 | | 7 | exp Headache disorders/ | 35164 | | 8 | (cephalalgia\* or head ache\* or headache\* or migraine\*).ti,ab,kf. | 107342 | | 9 | or/6-8 | 118816 | | 10 | 5 and 9 | 641 | | |

2. Embase

|  |  |
| --- | --- |
| Interface: embase.com  Date of Search: 26 January 2021  Number of hits: 3,402  Comment: Emtree is the controlled vocabulary in Embase | Field labels   * /exp = exploded Emtree term * /de = non exploded Emtree term * ti,ab = title and abstract * NEAR/x = within x words, regardless of order * \* = truncation of word for alternate endings |
| Embase Session Results  |  |  |  | | --- | --- | --- | | **#1** | **'attention deficit disorder'**/exp | 64,750\* | | **#2** | ((**attention\*** OR **hyperactiv\*** OR **inattention\***) NEAR/3 (**deficit\*** OR **disabilit\*** OR **disorder\***)):ti,ab,kw | 48,571\* | | **#3** | **hyperactivity**:ti,ab,kw AND (**inattention**:ti,ab,kw OR **attention**:ti,ab,kw) | 38,524\* | | **#4** | **addh**:ti,ab,kw OR **adhd**:ti,ab,kw OR **hyperkinetic\*** | 43,929\* | | **#5** | #1 OR #2 OR #3 OR #4 | 83,766\* | | **#6** | **'headache and facial pain'**/exp | 320,522\* | | **#7** | **cephalalgia\***:ti,ab,kw OR **'head ache\*'**:ti,ab,kw OR **headache\***:ti,ab,kw OR **migraine\***:ti,ab,kw | 168,666\* | | **#8** | #6 OR #7 | 346,268\* | | **#9** | #5 AND #8 | 3,402 | | |

3. Psycinfo

|  |  |
| --- | --- |
| Interface: Ovid  Date of Search: 26 January 2021  Number of hits: 307  Comment: In Ovid, two or more words are automatically searched as phrases; i.e. no quotation marks are needed | Field labels   * exp/ = exploded controlled term * / = non exploded controlled term * .ti,ab,id. = title, abstract and author keywords * adjx = within x words, regardless of order * \* = truncation of word for alternate endings |
| Database(s): **PsycINFO**1806 to January Week 4 2021 Search Strategy:   |  |  |  | | --- | --- | --- | | **#** | **Searches** | **Results** | | 1 | exp attention deficit disorder/ | 27923 | | 2 | ((attention or hyperactiv\* or inattention) adj3 (deficit\* or disabilit\* or disorder\*)).ti,ab,id. | 36533 | | 3 | (hyperactivity and (attention or inattention)).ti,ab,id. | 31150 | | 4 | (addh or adhd or hyperkinetic\*).ti,ab,id. | 30390 | | 5 | or/1-4 | 44297 | | 6 | exp headache/ | 15480 | | 7 | (cephalalgia\* or head ache\* or headache\* or migraine\*).ti,ab,id. | 23606 | | 8 | or/6-7 | 23725 | | 9 | 5 and 8 | 307 | | |

**eInclusion articles 1.** Studies/citations retained for review question 1 in the present systematic reivew

1. **Akmatov 2021**

Akmatov MK, Ermakova T, Bätzing J. Psychiatric and Nonpsychiatric Comorbidities Among Children With ADHD: An Exploratory Analysis of Nationwide Claims Data in Germany. *J Atten Disord*. 2021; 25(6), 874–884. doi: 10.1177/1087054719865779.

1. **Alabaf 2019**

Alabaf S, Gillberg C, Lundström S, et al. Physical health in children with neurodevelopmental disorders. *J Autism Dev Disord*. 2019;49(1):83-95. doi: 10.1007/s10803-018-3697-4.

1. **Arruda 2010**

Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Migraine, tension-type headache, and attention-deficit/hyperactivity disorder in childhood: a population-based study. *Postgrad Med*. 2010;122(5):18-26. doi: 10.3810/pgm.2010.09.2197.

1. **Arruda 2020**

Arruda MA, Arruda R, Guidetti V, Bigal ME. ADHD Is Comorbid to Migraine in Childhood: A Population-Based Study. *J Atten Disord*. 2020;24(7):990-1001. doi: 10.1177/1087054717710767.

1. **Cuffe 2009**

Cuffe SP, Moore CG, McKeown R. ADHD and health services utilization in the national health interview survey. *J Atten Disord*. 2009;12(4):330-340. doi: 10.1177/1087054708323248.

1. **Holmberg 2006**

Holmberg K, Hjern A. Health complaints in children with attention-deficit/hyperactivity disorder. *Acta Paediatr*. 2006;95(6):664-670. doi: 10.1080/08035250600717121.

1. **Jameson 2016**

Jameson ND, Sheppard BK, Lateef TM, Vande Voort JL, He JP, Merikangas KR. Medical Comorbidity of Attention-Deficit/Hyperactivity Disorder in US Adolescents. *J Child Neurol*. 2016;31(11):1282-1289. doi: 10.1177/0883073816653782.

1. **Kaplan 1987**

Kaplan BJ, McNicol J, Conte RA, Moghadam HK. Physical signs and symptoms in preschool-age hyperactive and normal children. *J Dev Behav Pediatr*. 1987;8(6):305-310.

1. **Kutuk 2018**

Kutuk MO, Tufan AE, Guler G, et al. Migraine and associated comorbidities are three times more frequent in children with ADHD and their mothers. *Brain Dev*. 2018;40(10):857-864. doi: 10.1016/j.braindev.2018.06.001.

1. **Lateef 2009**

Lateef TM, Merikangas KR, He J, Kalaydjian A, Khoromi S, Knight E, Nelson KB. Headache in a national sample of American children: prevalence and comorbidity. *J Child Neurol*. 2009;24(5):536-543. doi: 10.1177/0883073808327831.

1. **Law 2019**

Law EF, Palermo TM, Zhou C, Groenewald CB. Economic Impact of Headache and Psychiatric Comorbidities on Healthcare Expenditures Among Children in the United States: A Retrospective Cross-Sectional Study. *Headache*. 2019;59(9):1504-1515. doi: 10.1111/head.13639.

1. **Schieve 2012**

Schieve LA, Gonzalez V, Boulet SL, et al. Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006-2010. *Res Dev Disabil*. 2012;33(2):467-476. doi: 10.1016/j.ridd.2011.10.008.

1. **Strine 2006**

Strine TW, Okoro CA, McGuire LC, Balluz LS. The associations among childhood headaches, emotional and behavioral difficulties, and health care use. Pediatrics. 2006;117(5):1728-1735. doi: 10.1542/peds.2005-1024.

**eExclusion reasons 1.** Studies/citations discarded after assessing their full text for review question 1, with reasons for exclusions.

**Review question 1: Does the prevalence of headache differ between children and adolescents with and without ADHD?**

1. **Aggarwal 2020**

Aggarwal SS, Ott SD, Padhye NS, Schulz PE. Sex, race, ADHD, and prior concussions as predictors of concussion recovery in adolescents. *Brain Inj*. 2020;34(6):809-817. doi: 10.1080/02699052.2020.1740942.

*Reason for exclusion: Target population was not ADHD*

1. **Al-Haidar 2003**

Al-Haidar FA. Inpatient child and adolescent psychiatric referrals in Saudi Arabia: clinical profiles and treatment. *East Mediterr Health J.* 2003;9(5-6):996-1002.

*Reason for exclusion: Target population was not ADHD*

1. **Al-Sharbati 2003**

Al-Sharbati MM, Al-Hussaini AA, Antony SX. Profile of child and adolescent psychiatry in Oman. *Saudi Med J*. 2003;24(4):391-395.

*Reason for exclusion: Target population was not ADHD*

1. **Anttila 2004**

Anttila P, Sourander A, Metsähonkala L, Aromaa M, Helenius H, Sillanpää M. Psychiatric symptoms in children with primary headache. *J Am Acad Child Adolesc Psychiatry*. 2004;43(4):412-419. doi: 10.1097/00004583-200404000-00007.

*Reason for exclusion: No diagnosis of ADHD*

1. **Arruda 2014**

Arruda MA, Arruda R. Psychological adjustment in children with episodic migraine: a population-based study. *Psychol Neurosci*. 2014;7(1),33-41. doi: 10.3922/j.psns.2014.1.06

*Reason for exclusion: No diagnosis of ADHD; same dataset as Arruda 2017.*

1. **Arruda 2012**

Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: association with school performance. *Neurology*. 2012;79(18):1881-1888. doi: 10.1212/WNL.0b013e318271f812.

*Reason for exclusion: No diagnosis of ADHD; same dataset as Arruda 2017.*

1. **Bai 2017**

Bai G, Herten MH, Landgraf JM, Korfage IJ, Raat H. Childhood chronic conditions and health-related quality of life: Findings from a large population-based study. *PLoS One*. 2017;12(6):e0178539. doi: 10.1371/journal.pone.0178539.

*Reason for exclusion: No specific question used to obtain the diagnosis of ADHD*

1. **Bansal 2011**

Bansal PD, Barman R. Psychopathology of school going children in the age group of 10-15 years. *Int J Appl Basic Med Res*. 2011;1(1):43-47. doi: 10.4103/2229-516X.81980.

*Reason for exclusion: No data of comorbidity of ADHD and headache provided*

1. **Battistutta 2009**

Battistutta S, Aliverti R, Montico M, Zin R, Carrozzi M. Chronic tension-type headache in adolescents. Clinical and psychological characteristics analyzed through self- and parent-report questionnaires. *J Pediatr Psychol*. 2009;34(7):697-706. doi: 10.1093/jpepsy/jsn102.

*Reason for exclusion: No diagnosis of ADHD*

1. **Beales 2012**

Beales DJ, Smith AJ, O'Sullivan PB, Straker LM. Low back pain and comorbidity clusters at 17 years of age: a cross-sectional examination of health-related quality of life and specific low back pain impacts. *J Adolesc Health*. 2012;50(5):509-516. doi: 10.1016/j.jadohealth.2011.09.017.

*Reason for exclusion: No diagnosis of ADHD*

1. **Blaauw 2014**

Blaauw BA, Dyb G, Hagen K, et al. Anxiety, depression and behavioral problems among adolescents with recurrent headache: the Young-HUNT study. *J Headache Pain*. 2014;15(1):38. doi: 10.1186/1129-2377-15-38.

*Reason for exclusion: No diagnosis of ADHD*

1. **Blackman 2011**

Blackman JA, Gurka MJ, Gurka KK, Oliver MN. Emotional, developmental and behavioural co-morbidities of children with chronic health conditions. *J Paediatr Child Health*. 2011;47(10):742-747. doi: 10.1111/j.1440-1754.2011.02044.x.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Bruijn 2009**

Bruijn J, Arts WF, Duivenvoorden H, Dijkstra N, Raat H, Passchier J. Quality of life in children with primary headache in a general hospital. *Cephalalgia*. 2009;29(6):624-630. doi: 10.1111/j.1468-2982.2008.01774.x.

*Reason for exclusion: No data of comorbidity of ADHD and headache provided*

1. **Bursztein 2006**

Bursztein C, Steinberg T, Sadeh A. Sleep, sleepiness, and behavior problems in children with headache. *J Child Neurol*. 2006;21(12):1012-1019. doi: 10.1177/7010.2006.00239.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Carpenet 2019**

Carpenet C, Guichard E, Tzourio C, Kurth T. Self-perceived attention deficit and hyperactivity symptom levels and risk of non-migraine and migraine headaches among university students: A cross-sectional study. *Cephalalgia*. 2019;39(6):711-721. doi: 10.1177/0333102418804155.

*Reason for exclusion: Target population was adults*

1. **Carter-Pokras 2019**

Carter-Pokras OD, Bugbee BA, Gold RS, Lauver PE, Aiken R, Arria AM. Utilizing Student Health and Academic Data: A County-Level Demonstration Project. *Health Promot Pract*. Published online Aug 9, 2019. doi: 10.1177/1524839919862796.

*Reason for exclusion: No data of comorbidity of ADHD and headache provided*

1. **Cook 2020**

Cook NE, Sapigao RG, Silverberg ND, et al. Attention-Deficit/Hyperactivity Disorder Mimics the Post-concussion Syndrome in Adolescents. *Front Pediatr*. 2020;8:2. doi: 10.3389/fped.2020.00002.

*Reason for exclusion: No comparison group; ADHD was identified by self-report questionnaires*

1. **Del Bene 1982**

Del Bene E. Multiple aspects of headache risk in children. *Adv Neurol*. 1982;33:187-198.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Egger 1998**

Egger HL, Angold A, Costello EJ. Headaches and psychopathology in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1998;37(9):951-958. doi: 10.1097/00004583-199809000-00015.

*Reason for exclusion: No baseline data provided*

1. **Egger 1999**

Egger HL, Costello EJ, Erkanli A, Angold A. Somatic complaints and psychopathology in children and adolescents: stomach aches, musculoskeletal pains, and headaches*. J Am Acad Child Adolesc Psychiatry*. 1999;38(7):852-860. doi: 10.1097/00004583-199907000-00015.

*Reason for exclusion: No baseline data provided*

1. **Fasmer 2012**

Fasmer OB, Riise T, Lund A, Dilsaver SC, Hundal O, Oedegaard KJ. Comorbidity of migraine with ADHD. *J Atten Disord*. 2012;16(4):339-345. doi: 10.1177/1087054710385784.

*Reason for exclusion: Target population was ADHD with pharmacological treatment*

1. **Frank-Briggs 2011**

Frank-Briggs AI, D Alikor EA. Pattern of paediatric neurological disorders in port harcourt, Nigeria. *Int J Biomed Sci*. 2011;7(2):145-149.

*Reason for exclusion: No diagnosis of ADHD and headache*

1. **Galli 2007**

Galli F, D'Antuono G, Tarantino S, et al. Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL). *Cephalalgia*. 2007;27(3):211-219. doi: 10.1111/j.1468-2982.2006.01271.x.

*Reason for exclusion: No diagnosis of ADHD*

1. **Genizi 2013**

Genizi J, Gordon S, Kerem NC, Srugo I, Shahar E, Ravid S. Primary headaches, attention deficit disorder and learning disabilities in children and adolescents. *J Headache Pain*. 2013;14(1):54. doi: 10.1186/1129-2377-14-54.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Genizi 2016**

Genizi J, Marom D, Srugo I, Kerem NC. The Relations between Attention Deficit Hyperactivity Disorder and Headaches in a Non-Clinical Sample of Adolescents. *Acad J Ped Neonatol*. 2016;2(2):555583. doi: 10.19080/AIBM.2016.02.555583

*Reason for exclusion: ADHD was identified by self-report questionnaires*

1. **Ghandour 2010**

Ghandour RM, Kogan MD, Blumberg SJ, Perry DF. Prevalence and correlates of internalizing mental health symptoms among CSHCN. *Pediatrics*. 2010;125(2):e269-e277. doi: 10.1542/peds.2009-0622.

*Reason for exclusion: No data of comorbidity of ADHD and headache provided*

1. **Gladstein 1996**

Gladstein J, Holden EW. Chronic daily headache in children and adolescents: a 2-year prospective study. *Headache*. 1996;36(6):349-351. doi: 10.1046/j.1526-4610.1996.3606349.x.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Groenewald 2015**

Groenewald CB, Wright DR, Palermo TM. Health care expenditures associated with pediatric pain-related conditions in the United States. *Pain*. 2015;156(5):951-957. doi: 10.1097/j.pain.0000000000000137.

*Reason for exclusion: No data of comorbidity of ADHD and headache provided*

1. **Güler 2017**

Güler G, Kütük MÖ, Toros F, Özge A, Taşdelen BJ. The high level of psychiatric disorders associated with migraine or tension-type headache in adolescents. *J Neurol Sci*. 2017;34(4):312-321. doi: 10.24165/jns.10112.17

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Halfon 2013**

Halfon N, Larson K, Slusser W. Associations between obesity and comorbid mental health, developmental, and physical health conditions in a nationally representative sample of US children aged 10 to 17. *Acad Pediatr*. 2013;13(1):6-13. doi: 10.1016/j.acap.2012.10.007.

*Reason for exclusion: Target population was not ADHD; no data of comorbidity of ADHD and headache provided*

1. **Haynes 2015**

Haynes V, Lopez-Romero P, Anand E. Attention-deficit/hyperactivity disorder Under Treatment Outcomes Research (AUTOR): a European observational study in pediatric subjects. *Atten Defic Hyperact Disord*. 2015;7(4):295-311. doi: 10.1007/s12402-015-0177-y.

*Reason for exclusion: Target population was individuals with ADHD receiving pharmacological treatment*

1. **Holmberg 2010**

Holmberg K. The association of bullying and health complaints in children with attention-deficit/hyperactivity disorder. *Postgrad Med*. 2010;122(5):62-68. doi: 10.3810/pgm.2010.09.2202.

*Reason for exclusion: Same dataset as Holmberg 2006*

1. **Hughes 2021**

Hughes A, Wade KH, Dickson M, et al. Common health conditions in childhood and adolescence, school absence, and educational attainment: Mendelian randomization study. *NPJ Sci Learn*. 2021;6(1):1. doi: 10.1038/s41539-020-00080-6.

*Reason for exclusion: Target population was not ADHD; No diagnosis of ADHD*

1. **Hvidberg 2020**

Hvidberg MF, Johnsen SP, Davidsen M, Ehlers L. A Nationwide Study of Prevalence Rates and Characteristics of 199 Chronic Conditions in Denmark. *Pharmacoecon Open*. 2020;4(2):361-380. doi: 10.1007/s41669-019-0167-7.

*Reason for exclusion:* *The study population including both adolescents and adults; No data of comorbidity of ADHD and headache provided*

1. **Jacobs 2019**

Jacobs H, Pakalnis A. Premonitory Symptoms in Episodic and Chronic Migraine From a Pediatric Headache Clinic. *Pediatr Neurol*. 2019;97:26-29. doi: 10.1016/j.pediatrneurol.2019.03.023.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Jayaprakash 2012**

Jayaprakash R. Clinical profile of children and adolescents attending the behavioural paediatrics unit OPD in a tertiary care set up. *J Indian Assoc Child Adolesc Ment Health* 2012;8(3):51-66.

*Reason for exclusion: Target population was not ADHD; no data of comorbidity of ADHD and headache provided*

1. **Just 2003**

Just U, Oelkers R, Bender S, et al. Emotional and behavioural problems in children and adolescents with primary headache. *Cephalalgia*. 2003;23(3):206-213. doi: 10.1046/j.1468-2982.2003.00486.x.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Lateef 2019**

Lateef T, He JP, Nelson K, et al. Physical-Mental Comorbidity of Pediatric Migraine in the Philadelphia Neurodevelopmental Cohort. *J Pediatr*. 2019;205:210-217. doi: 10.1016/j.jpeds.2018.09.033.

*Reason for exclusion: The study population including both children and adults*

1. **Lee 2015**

Lee SM, Yoon JR, Yi YY, et al. Screening for depression and anxiety disorder in children with headache. *Korean J Pediatr*. 2015;58(2):64-68. doi: 10.3345/kjp.2015.58.2.64.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Liakopoulou-Kairis 2002**

Liakopoulou-Kairis M, Alifieraki T, Protagora D, et al. Recurrent abdominal pain and headache--psychopathology, life events and family functioning. *Eur Child Adolesc Psychiatry*. 2002;11(3):115-122. doi: 10.1007/s00787-002-0276-0.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Liu 2018**

Liu T, Lingam R, Lycett K, et al. Parent-reported prevalence and persistence of 19 common child health conditions. *Arch Dis Child*. 2018;103(6):548-556. doi: 10.1136/archdischild-2017-313191.

*Reason for exclusion: No data of comorbidity of ADHD and headache provided*

1. **Lollar 2012**

Lollar DJ, Hartzell MS, Evans MA. Functional difficulties and health conditions among children with special health needs. *Pediatrics*. 2012;129(3):e714-e722. doi: 10.1542/peds.2011-0780.

*Reason for exclusion: No diagnosis of ADHD*

1. **Machnes-Maayan 2014**

Machnes-Maayan D, Elazar M, Apter A, Zeharia A, Krispin O, Eidlitz-Markus T. Screening for psychiatric comorbidity in children with recurrent headache or recurrent abdominal pain. *Pediatr Neurol*. 2014;50(1):49-56. doi: 10.1016/j.pediatrneurol.2013.07.011.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Mahaj 2016**

Mahaj M, Sharkia R, Shorbaji N, Zelnik N. Clinical Profile of Attention Deficit Hyperactivity Disorder: Impact of Ethnic and Social Diversities in Israel. *Isr Med Assoc J*. 2016;18(6):322-325.

*Reason for exclusion: No comparison group; headache was measures as a side effect of ADHD medication*

1. **Mahajnah 2020**

Mahajnah M, Sharkia R, Shorbaji N, Zelnik N. The Clinical Characteristics of ADHD Diagnosed in Adolescents in Comparison With Younger Children. *J Atten Disord*. 2020;24(8):1125-1131. doi: 10.1177/1087054717696768.

*Reason for exclusion: No comparison group; headache was measures as a side effect of ADHD medication*

1. **Mazzone 2006**

Mazzone L, Vitiello B, Incorpora G, Mazzone D. Behavioural and temperamental characteristics of children and adolescents suffering from primary headache. *Cephalalgia*. 2006;26(2):194-201. doi: 10.1111/j.1468-2982.2005.01015.x.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Milde-Busch 2010**

Milde-Busch A, Boneberger A, Heinrich S, et al. Higher prevalence of psychopathological symptoms in adolescents with headache. A population-based cross-sectional study. *Headache*. 2010;50(5):738-748. doi: 10.1111/j.1526-4610.2009.01605.x.

*Reason for exclusion: No diagnosis of ADHD; no data of comorbidity of ADHD and headache provided*

1. **Mitchell 2019**

Mitchell BL, Campos AI, Rentería ME, et al. Twenty-Five and Up (25Up) Study: A New Wave of the Brisbane Longitudinal Twin Study. *Twin Res Hum Genet*. 2019;22(3):154-163. doi: 10.1017/thg.2019.27.

*Reason for exclusion: Study population was adults*

1. **Muzina 2011**

Muzina DJ, Chen W, Bowlin SJ. A large pharmacy claims-based descriptive analysis of patients with migraine and associated pharmacologic treatment patterns. *Neuropsychiatr Dis Treat*. 2011;7:663-672. doi: 10.2147/NDT.S25463.

*Reason for exclusion: No diagnosis of ADHD*

1. **Needham 2010**

Needham B, Hill TD. Do gender differences in mental health contribute to gender differences in physical health? *Soc Sci Med*. 2010;71(8):1472-1479. doi: 10.1016/j.socscimed.2010.07.016.

*Reason for exclusion: Study population was adults*

1. **Operto 2018**

Operto FF, Craig F, Peschechera A, Mazza R, Lecce PA, Margari L. Parenting Stress and Emotional/Behavioral Problems in Adolescents with Primary Headache. *Front Neurol*. 2018;8:749. doi: 10.3389/fneur.2017.00749.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Pakalnis 2005**

Pakalnis A, Gibson J, Colvin A. Comorbidity of psychiatric and behavioral disorders in pediatric migraine. *Headache*. 2005;45(5):590-596. doi: 10.1111/j.1526-4610.2005.05113.x.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Pakalnis 2008**

Pakalnis A, Tischner J, Colvin A, Kring D. Emotional and behavioral disorders in pediatric episodic tension headaches. *J Pediatr Neurol*. 2008;6(2):109-113

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Park 2017**

Park KJ, Lee JS, Kim HW. Medical and Psychiatric Comorbidities in Korean Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. *Psychiatry Investig*. 2017;14(6):817-824. doi: 10.4306/pi.2017.14.6.817

*Reason for exclusion: No measurement of headache*

1. **Pavone 2012**

Pavone P, Rizzo R, Conti I, et al. Primary headaches in children: clinical findings on the association with other conditions. *Int J Immunopathol Pharmacol*. 2012;25(4):1083-1091. doi: 10.1177/039463201202500425.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Pitrou 2010**

Pitrou I, Shojaei T, Chan-Chee C, Wazana A, Boyd A, Kovess-Masféty V. The associations between headaches and psychopathology: a survey in school children. *Headache*. 2010;50(10):1537-1548. doi: 10.1111/j.1526-4610.2010.01781.x.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Reale 2011**

Reale L, Guarnera M, Grillo C, Maiolino L, Ruta L, Mazzone L. Psychological assessment in children and adolescents with Benign Paroxysmal Vertigo. *Brain Dev*. 2011;33(2):125-130. doi: 10.1016/j.braindev.2010.03.006.

*Reason for exclusion: Target population was not ADHD; no diagnosis of ADHD*

1. **Riva 2012**

Riva D, Usilla A, Aggio F, Vago C, Treccani C, Bulgheroni S. Attention in children and adolescents with headache. *Headache*. 2012;52(3):374-384. doi: 10.1111/j.1526-4610.2011.02033.x.

*Reason for exclusion: Target population was not ADHD; no diagnosis of ADHD*

1. **Romano 2020**

Romano C, Cho SY, Marino S, Raucci U, Fiumara A, Falsaperla R, Massimino CR, Taibi R, Greco F, Venti V, Sullo F, Fontana A, Rizzo R, Pustorino E, Jin DK, Pavone P. Primary headache in childhood associated with psychiatric disturbances: an update. *Eur Rev Med Pharmacol Sci*. 2020;24(12):6893-6898. doi: 10.26355/eurrev\_202006\_21680.

*Reason for exclusion: Target population was not ADHD; No clear information on the method of ADHD identification*

1. **Salvadori 2007**

Salvadori F, Gelmi V, Muratori F. Present and previous psychopathology of juvenile onset migraine: a pilot investigation by Child Behavior Checklist. *J Headache Pain*. 2007;8(1):35-42. doi: 10.1007/s10194-007-0334-y.

*Reason for exclusion: Target population was not ADHD; no diagnosis of ADHD*

1. **Sarioglu 2003**

Sarioglu B, Erhan E, Serdaroglu G, Doering BG, Erermis S, TutuncuoGlu S. Tension-type headache in children: a clinical evaluation. *Pediatr Int*. 2003;45(2):186-189. doi: 10.1046/j.1442-200x.2003.01678.x.

*Reason for exclusion: Target population was not ADHD; no diagnosis of ADHD*

1. **Slater 2012**

Slater SK, Kashikar-Zuck SM, Allen JR, et al. Psychiatric comorbidity in pediatric chronic daily headache. *Cephalalgia*. 2012;32(15):1116-1122. doi: 10.1177/0333102412460776.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Tegethoff 2015**

Tegethoff M, Belardi A, Stalujanis E, Meinlschmidt G. Comorbidity of Mental Disorders and Chronic Pain: Chronology of Onset in Adolescents of a National Representative Cohort. *J Pain*. 2015;16(10):1054-1064. doi: 10.1016/j.jpain.2015.06.009.

*Reason for exclusion: No comparison group*

1. **Trangkasombat 2008**

Trangkasombat U. Clinical characteristics of ADHD in Thai children. *J Med Assoc Thai*. 2008;91(12):1894-1898.

*Reason for exclusion: No measurement of headache; no comparison group*

1. **Uçar 2020**

Uçar HN, Tekin U, Tekin E. Irritability and its relationships with psychological symptoms in adolescents with migraine: a case-control study. *Neurol Sci*. 2020;41(9):2461-2470. doi: 10.1007/s10072-020-04331-7.

*Reason for exclusion: Target population was not ADHD; no diagnosis of ADHD*

1. **Wade 2008**

Wade TJ, Mansour ME, Line K, Huentelman T, Keller KN. Improvements in health-related quality of life among school-based health center users in elementary and middle school. *Ambul Pediatr*. 2008;8(4):241-249. doi: 10.1016/j.ambp.2008.02.004.

*Reason for exclusion: No measurement of headache*

1. **Wagner 2015**

Wagner JL, Wilson DA, Smith G, Malek A, Selassie AW. Neurodevelopmental and mental health comorbidities in children and adolescents with epilepsy and migraine: a response to identified research gaps. *Dev Med Child Neurol*. 2015;57(1):45-52. doi: 10.1111/dmcn.12555.

*Reason for exclusion: Target population was not ADHD; no comparison group*

1. **Valeriani 2009**

Valeriani M, Galli F, Tarantino S, et al. Correlation between abnormal brain excitability and emotional symptomatology in paediatric migraine. *Cephalalgia*. 2009;29(2):204-213. doi: 10.1111/j.1468-2982.2008.01708.x.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Vannatta 2008**

Vannatta K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. Multiple perspectives on the psychological functioning of children with and without migraine. *Headache*. 2008;48(7):994-1004. doi: 10.1111/j.1526-4610.2007.01051.x.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

1. **Warfield 2018**

Warfield ME, Adams RS, Ritter GA, Valentine A, Williams TV, Larson MJ. Health care utilization among children with chronic conditions in military families. *Disabil Health J*. 2018;11(4):624-631. doi: 10.1016/j.dhjo.2018.06.002.

*Reason for exclusion:* *No data of comorbidity of ADHD and headache provided*

1. **Whiteford 2015**

Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PLoS One*. 2015;10(2):e0116820. doi: 10.1371/journal.pone.0116820.

*Reason for exclusion: The study population including both children and adults*

1. **Vigo 2020**

Vigo D, Jones L, Thornicroft G, Atun R. Burden of Mental, Neurological, Substance Use Disorders and Self-Harm in North America: A Comparative Epidemiology of Canada, Mexico, and the United States. *Can J Psychiatry*. 2020;65(2):87-98. doi: 10.1177/0706743719890169.

*Reason for exclusion: The study population including both children and adults*

1. **Wittchen 2011**

Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(9):655-679. doi: 10.1016/j.euroneuro.2011.07.018.

*Reason for exclusion: The study population including both children and adults*

1. **Öztop 2016**

Öztop DB, Taşdelen Bİ, PoyrazoğLu HG, et al. Assessment of Psychopathology and Quality of Life in Children and Adolescents With Migraine. *J Child Neurol*. 2016;31(7):837-842. doi: 10.1177/0883073815623635.

*Reason for exclusion: No diagnosis of ADHD; target population was not ADHD; no comparison group*

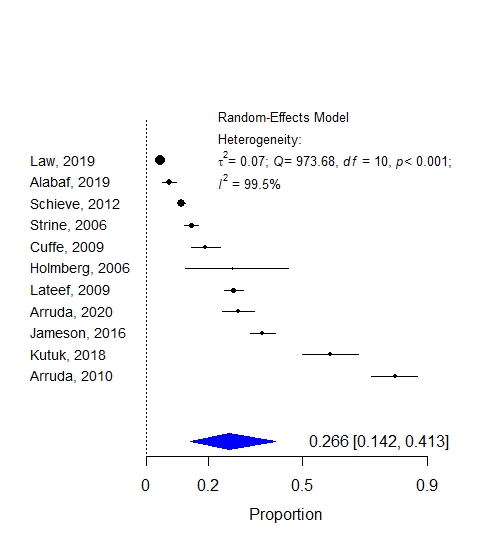
**eTable 1.** Summary of characteristics of included case-control/cross-sectional studies (*n* = 13)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Country, Recruitment/Dataset | Participants (male%) | Age range in years (Mean) | Diagnostic assessment | | Headache type | Matching/  Adjustment | Odds  ratio | the Newcastle-Ottawa Scale | | | | | | | |
| ADHD | Headache | S1 | S2 | S3 | S4 | C1 | E1 | E2 | E3 |
| Akmatov (2021) | Germany, data of health insurance | ADHD: n = 258,662 (75.6); Control: n = 2,327,958 (75.6) | 5-14 (NR) | ICD-10 | ICD-10 | Migraine | Age, sex, region matched | 2.49 (2.37-2.61) | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 1 |
| Alabaf (2019) | Sweden, CATSS | ADHD: n = 586 (NR); Control: n = 27,472 (NR) | 9, 12 | A-TAC | Parent report | Migraine | N/A | 2.23 (1.62-3.06) | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 |
| Arruda (2010) | Brazil, Attention–Brazil Project | ADHD: n = 114 (64.9); Control: n = 1,742 (50.8) | 5-12 (NR) | SNAP-IV, CBCL | Parent report  (the ICHD-2 criteria) | Migraine, Tension headache | N/A | 0.90 (0.56-1.44) | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Arruda (2020) | Brazil, Learning Child | ADHD: n = 303 (71.3); Control: n = 5,368 (50.8) | 5-12 (NR) | SNAP-IV, SDQ | Parent report  (the ICHD-2 criteria) | Migraine, Tension headache | N/A | 1.47 (1.14-1.90) | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Cuffe (2009) | USA,  2001 NHIS | ADHD: n = 278 (69.8); Control: n = 9,243 (50.8) | 4-17 (NR) | SDQ | Parent report | Migraine/headache | N/A | 3.37 (2.47-4.60) | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Holmberg (2006) | Sweden, school students | ADHD: n = 29 (82.8); Control: n = 487 (49.3) | 9-13 (NR) | DSM-IV, Conner-10 items | Self-report | Headache | N/A | 1.06 (0.46-2.45) | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Jameson (2016) | USA,  NCS-A | ADHD: n = 550 (NR); Control: n = 5,933 (NR) | 13-18 (15.2) | DSM-IV | Self-/parent- report | Migraine/headache | Adjusted for age, sex, race, parental education | 1.46 (1.07-1.98) | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 0 |
| Kaplan (1987)a | Canada, hospital | ADHD: n = 40 (75.0); Control: n = 40 (75.0) | 3.5-6 (NR) | DSM-III | Parent report | Headache | Age, sex matched | 14.79 (1.81-121.14) | 1 | 0 | 1 | 1 | 2 | 0 | 1 | 0 |
| Kutuk (2018) | Turkey, hospital | ADHD: n = 117 (82.1); Control: n = 111 (76.6) | 6-18 (NR) | DSM-5 | Clinical diagnosis | Migraine, Tension headache | Age, sex matched | 2.36 (1.39-4.02) | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 0 |
| Lateef (2009) | USA, NHANES | ADHD: n = 899 (NR); Control: n = 10019 (NR) | 4-18 (NR) | Question-naire | Parent-report | Migraine/headache | Adjusted for sex, age, race, income | 2.03 (1.74-2.37) | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 0 |
| Law (2019) | USA,  2012-2015 MEPS | ADHD: n = 2,248 (NR); Control: n = 32,385 (NR) | 2-17 (NR) | Parent report, healthcare providers | Parent-report, healthcare providers | Headache | N/A | 2.25 (1.82-2.78) | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| Schieve (2012) | USA,  2006-2010 NHIS | ADHD: n = 2,901 (70.4); Control: n = 35,775 (48.8) | 3-17 (NR) | Question-naire | Parent-report | Migraine/headache | Adjusted for age, sex, race, maternal education | 2.55 (2.26-2.89) | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 0 |
| Strine (2006) | USA,  2003 NHIS | ADHD: n = 879 (70.4); Control: n = 8,385 (48.8) | 4-17 (NR) | SDQ | Parent-report | Headache | Adjusted for age, sex, race, and otherb | 2.70 (2.19-3.32) | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 0 |

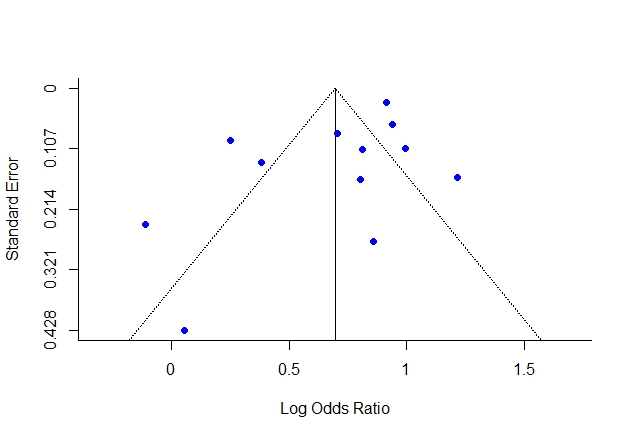
N/A, Not applicable; NR, Not reported; CATSS, Child and Adolescent Twin Study in Sweden; A-TAC, the Autism-Tics, ADHD and other Comorbidities; ASD, Autism spectrum disorder; LD, Learning disorder; ICHD, International Classification of Headache Disorders; SDQ, the Strengths and Difficulties Questionnaire; NHIS, National Health Interview Survey; NCS-A, the National Comorbidity Survey Replication-Adolescent Supplement; NHANES, the National Health and Nutrition Examination Surveys; MEPS, Medical Expenditure Panel Surveys;

aOnly study 1 was eligible by the inclusion criteria; however, the data in this study were not included in the meta-analysis due to the outlying odds ratio

bParental structure (single parent household, both parents, and neither parent.), poverty status, type of health care coverage, and number of comorbid conditions.

**eFigure 1.** Caterpillar plot of pooled prevalence of overall headache in children with ADHD

**eFigure 2.** Funnel plot of epidemiological studies on the association between ADHD and headache among children



Egger's test: *t* = -1.79, *df* = 10, *p* = 0.104

**eIncluded articles 2.** Studies/citations retained for review question 2 in the present meta-analysis

**Review question 2: Is the use of common medications for ADHD associated with headache in children and adolescents?**

**1. Allen2005, B4Z-MC-LYAS**

* Lewis D, Linder S, Kurlan R, et al. Atomoxetine for the treatment of attention deficit hyperactivity disorder and comorbid tics in children. *Ann Neurol.* 2003;54(Suppl. 7):S106.
* Bangs ME, Allen AJ, Kurlan R, et al. Atomoxetine treatment in children with attention-deficit/hyperactivity disorder and comorbid TIC disorders. *Int J Neuropsychopharmacol*. 2004;7:S441.
* Coffey BJ, Kelsey DK, Feldman PD, et al. Atomoxetine treatment in children with ADHD and comorbid tic disorders. *157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, NY 2004.*
* Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology.* 2005;65(12):1941-1949.
* Post hoc subgroup analysis in: Spencer TJ, Sallee FR, Gilbert DL, et al. Atomoxetine treatment of ADHD in children with comorbid Tourette syndrome. *J Atten Disord.* 2008;11(4):470-481.
* Pooled in: Newcorn JH, Sutton VK, Zhang S, et al. Characteristics of placebo responders in pediatric clinical trials of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2009;48(12):1165-1172.
* Commentary in: Anonymous. Atomoxetine may improve tic severity in children with ADHD, Tourette syndrome. *Brown university child & adolescent psychopharmacology update.* 2017;10(3):1, 6-7
* https://assets.contentful.com/hadumfdtzsru/5dD90Njz9uwIc2k00aEASe/ecc2afee105479b66fcc818a322d997d/Atomoxetine-B4Z-MC-LYAS.pdf

**2. Bangs2007, B4Z-MC-LYAX**

* Bangs ME, Emslie GJ, Spencer TJ, et al. A study of atomoxetine in adolescents with ADHD and comorbid depression. *45th Annual NCDEU (New Clinical Drug Evaluation Unit) Meeting; 2005 June 6 - 9; Boca Raton, FL.* *2005*:184.
* Bangs ME, Emslie GJ, Spencer TJ, et al. Efficacy and safety of atomoxetine in adolescents with attentiondeficit/hyperactivity disorder and major depression. *J Child Adolesc Psychopharmacol.* 2007;17(4):407-420.
* Pooled in: Newcorn JH, Sutton VK, Zhang S, et al. Characteristics of placebo responders in pediatric clinical trialsof attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2009;48(12):1165-1172.
* http://art45-paediatric-studies-docs.ema.europa.eu/GROUP%20A/Atomoxetine/atomoxetine%20B4Z-MCLYAX%20-%20clinical%20study%20summary.pdf https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2002/21-411\_Strattera.cfm

**3. Bangs2008 , B4Z-MC-LYBX, NCT00191698**

* Bangs ME, Hazell P, Danckaerts M, et al. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder and oppositional defiant disorder. [Erratum appears in *Pediatrics*. 2008;122(1): 227]. *Pediatrics.* 2008;121(2):e314-320.
* Post hoc analysis in: Hazell P, Becker K, Nikkanen EA, et al. Relationship between atomoxetine plasma concentration, treatment response and tolerability in attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *Atten Defic Hyperact Disord.* 2009;1(2):201-210.
* https://clinicaltrials.gov/ct2/show/NCT00191698
* https://assets.contentful.com/hadumfdtzsru/1S1dKYi8huoyqCecagkagQ/eff47adc1fb45190a286081c7b731169/Atomoxetine-B4Z-MC-LYBX.pdf
* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2002/21-411\_Strattera.cfm

**4. Biederman2002, SLI 381-301**

* Lopez FA, Biederman J, Chandler M, Smith W, Boellner SW, Arnold LE. Randomized, controlled trial of a oncedaily amphetamine formulation, SLI381, in children with attention-deficit hyperactivity disorder. *Ann Neurol.* 2001;50(3):S96-S96.
* Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallelgroup study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2002;110(2 Pt 1):258-266.
* Findling RL, McCracken JT, Frazer N, Tulloch SJ. Time course of vital signs after once-daily adderall extended release in ADHD children. *156th Annual Meeting of the American Psychiatric Association; 2003 May 17-22; San* *Francisco, CA 2003:Nr649*
* Findling RL, Biederman J, Wilens TE, et al. Short- and long-term cardiovascular effects of mixed amphetamine salts extended release in children. *J Pediatr.* 2005;147(3):348-354.
* Pooled in: McGough JJ, Biederman J, Wigal SB, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2005;44(6):530-538.

**5. Biederman2005, Study 311 Cephalon**

* Biederman J, Swanson JM, Lopez FA. Modafinil improves adhd symptoms in children in a randomized, doubleblind, placebo-controlled study. *156th Annual Meeting of the American Psychiatric Association, May 17-22, San* *Francisco CA. 2003*:No. 36.
* Biederman J, Swanson JM, Wigal SB, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. *Pediatrics.* 2005;116(6):e777-784.
* Swanson JM, Boellner S, Rugino T, Sangal RB, Wigal SB. Pediatric formulation of modafinil effective in children and adolescents with adhd. *158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26;* *Atlanta, GA.2005*:No. 47.
* Pooled in: Wigal SB, Biederman J, Swanson JM, Yang R, Greenhill LL. Efficacy and safety of modafinil filmcoated tablets in children and adolescents with or without prior stimulant treatment for attentiondeficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim Care* *Companion J Clin Psychiatry.* 2006;8(6):352-360.
* Barry RJ, Clarke AR. Modafinil improves symptoms of ADHD compared with placebo in young people. *Evid Based Ment Health.* 2006;9(3):68.
* Pooled in: Biederman J, Pliszka SR. Modafinil improves symptoms of attention-deficit/hyperactivity disorder across subtypes in children and adolescents. *J Pediatr.* 2008;152(3):394-399.
* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/98/020717A\_Provigil.cfm
* Modafinil (CEP-1538) Tablets, Supplemental NDA 20-717/S-019, ADHD Indication Briefing Document for Psychopharmacologic Drugs Advisory Committee Meeting (Document provided by Dr Eric Konofal)

**6. Biederman2006b**

* Biederman J, Swanson JM, Lopez FA. Modafinil improves adhd symptoms in children in a randomized, doubleblind, placebo-controlled study. *156th Annual Meeting of the American Psychiatric Association, May 17-22, San* *Francisco CA. 2003*:No. 36.
* Swanson JM, Greenhill LL, Biederman J. Modafinil in children with ADHD: a randomized, placebo-controlled study. *156th Annual Meeting of the American Psychiatric Association; 2003 May 17-22; San Francisco, CA. 2003*:No. 44.
* Biederman J, Swanson JM, Boellner SW, Lopez E. Modafinil as therapy for ADHD in children: A 4-week, doubleblind, placebo-controlled study. *Eur Neuropsychopharmacol.* 2004;14, S3, S364.
* Swanson JM, Biederman J, Boelliner SW, Lopez FA. Modafinil as therapy for ADHD in children: A 4-week, doubleblind, placebo-controlled study. *J Psychopharmacol.* 2004;18(3, Suppl. S):A53.
* Biederman J, Swanson JM, Wigal SB, Boellner SW, Earl CQ, Lopez FA. A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. *J Clin Psychiatry.* 2006;67(5):727-735.

**7. Biederman2007, NRP104-301, NCT00248092**

* Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther.* 2007;29(3):450-463.
* Lopez FA, Ginsberg LD, Arnold V. Effect of lisdexamfetamine dimesylate on parent-rated measures in children aged 6 to 12 years with attention-deficit/hyperactivity disorder: a secondary analysis. *Postgrad Med.* 2008;120(3):89-102.
* Findling RL, Adeyi B, Chen G, et al. Clinical response and symptomatic remission in children treated with lisdexamfetamine dimesylate for attention-deficit/hyperactivity disorder. *CNS Spectr.* 2010(9):559-568.
* Pooled for a post hoc analysis in: Goodman D, Faraone SV, Adler LA, Dirks B, Hamdani M, Weisler R. Interpreting ADHD rating scale scores: Linking ADHD rating scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. *Primary Psychiatry.* 2010;17(3):44-52.
* Pooled for a post hoc analysis in: Waxmonsky JG, Waschbusch DA, Glatt SJ, Faraone SV. Prediction of placebo response in 2 clinical trials of lisdexamfetamine dimeslylate for the treatment of ADHD. *J Clin Psychiatry.* 2011;72(10):1366-1375.
* Post hoc analysis in: Jain R, Babcock T, Burtea T, et al. Efficacy of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder previously treated with methylphenidate: a post hoc analysis. *Child Adolesc* *Psychiatry Ment Health.* 2011;5(1):35. (NCT00556296)-
* Previous reference related to: Conference proceeding: Jain R, Babcock T, Burtea T, et al. Efficacy of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder and suboptimal response to methylphenidate. *163rd Annual Meeting of the American Psychiatric Association; 2010 May 22-26; New Orleans,* *LA* 2010.
* Jain R, Duncan D, Babcock T, et al. Lisdexamfetamine dimesylate (LDX) in children with ADHD after suboptimal response to methylphenidate. *Eur Child Adolesc Psychiatry.* 2011;20:S126-S127.
* Pooled for a post hoc analysis in: McGough JJ, Greenbaum M, Adeyi B, et al. Sex subgroup analysis of treatment response to lisdexamfetamine dimesylate in children aged 6 to 12 years with attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol.* 2012;32(1):138-140.
* Included in: Coghill D, Sorooshian S, Caballero B. Safety outcomes from the clinical development programme for lisdexamfetamine dimesylate: A prodrug stimulant for the treatment of attention-deficit/hyperactivity disorder. *Eur* *Child Adolesc Psychiatry*. 2013;1):S224.
* Post hoc analysis in: Childress AC, Arnold V, Adeyi B, et al. The effects of lisdexamfetamine dimesylate on emotional lability in children 6 to 12 years of age with ADHD in a double-blind placebo-controlled trial. *J Atten* *Disord.* 2014;18(2):123-132.
* Used in a post hoc analysis in: Weisler RH, Adler LA, Kollins SH, et al. Analysis of individual items on the attention deficit/hyperactivity disorder symptom rating scale in children and adults: The effects of age and sex in pivotal trials of lisdexamfetamine dimesylate. *Neuropsychiatr Dis Treat.* 2014;10:1-12.
* Lopez FA, Childress A, Adeyi B, et al. ADHD Symptom Rebound and Emotional Lability With Lisdexamfetamine Dimesylate in Children Aged 6 to 12 Years. *J Atten Disord.* 2017;21(1):52-61.
* https://clinicaltrials.gov/ct2/show/NCT00248092
* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2007/021977s000TOC.cfm

**8. Biederman2008, SPD503-301, NCT00152009**

* Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics.* 2008;121(1):e73-84.
* Open label continuation phase: Biederman J, Melmed RD, Patel A, McBurnett K, Donahue J, Lyne A. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. *CNS Spectr.* 2008;13(12):1047-1055.
* Pooled in: Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. *J Atten Disord.* 2010;13(5):532-538.
* Pooled in: Sallee FR, Kollins SH, Wigal TL. Efficacy of guanfacine extended release in the treatment of combined and inattentive only subtypes of attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2012;22(3):206-214.
* Pooled in: Huss M, McBurnett K, Cutler AJ, et al. Separating efficacy and sedative effects of guanfacine extended release in children and adolescents with ADHD from four randomized, controlled, phase 3 clinical trials. *Eur* *Psychiatry.* 2016;33:S76-S77.
* Pooled in: Huss M, McBurnett K, Cutler AJ, Hervás A, Bliss C, Gao J, Dirks B, Newcorn JH. Distinguishing the efficacy and sedative effects of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2019;29(3):432-443. and in Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. J Atten Disord. 2010;13(5):532-8.
* https://clinicaltrials.gov/ct2/show/NCT00152009
* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2009/022037\_intuniv\_toc.cfm
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**9. Block2009, B4Z-US-LYCC, NCT00486122**

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*Authors provided us with pre-cross over data*

Includes also participants from **Epstein2011 (NCT01238822) (**previously excluded from Cortese et al., Lancet Psychiatry 2018):

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*Note: this study was considered as excluded in Cortese et al. 2018 as that participants who entered the study were deemed to be responders to MPH; however, in the process of the present update, it appered clear that they were (at least) partially reponders. As such, consistently with other studies in cluded in Cortes et al., 2018, this study was included*

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**53. Swanson2006**

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* Pooled in: Wigal SB, Biederman J, Swanson JM, Yang R, Greenhill LL. Efficacy and safety of modafinil filmcoated tablets in children and adolescents with or without prior stimulant treatment for attentiondeficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim Care* *Companion J Clin Psychiatry.* 2006;8(6):352-360.
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**55. Wehmeier2012, B4Z-SB-LYDV, NCT00546910**

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* Post hoc analysis in: Weiss M, Wasdell M, Patin J. A post hoc analysis of d-threo-methylphenidate hydrochloride (focalin) versus d,l-threo-methylphenidate hydrochloride (ritalin). *J Am Acad Child Adolesc Psychiatry.* 2004;43(11):1415-1421.
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**57. Wigal2015, NCT01239030**

* Wigal SB, Nordbrock E, Adjei AL, Childress A, Kupper RJ, Greenhill L. Efficacy of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR™) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: A Phase III, Randomized, Double-Blind Study. *CNS Drugs.* 2015;29(4):331-40. doi: 10.1007/s40263-015-0241-3.
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**58. Wilens2015, SPD503-312, EUCTR2011-002221-21, NCT01081132**

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* Pooled in: Huss, M., Newcorn, J., Connor, D., Hervas, A., Werner-Kiechle, T., & Robertson, B. (2017). Efficacy of guanfacine extended release in children and adolescents with ADHD and comorbid oppositional defiant disorder. *European Neuropsychopharmacology, 27 (Supplement 4)*, S1114.
* https://clinicaltrials.gov/ct2/show/NCT01081132 **(**other ID: SPD503-312)
* https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\_number:2011-002221-21

**eExclusion reasons 2.** Studies/citations discarded after assessing their full text for review question 2, with reasons for exclusions.

**Review question 2: Is the use of common medications for ADHD associated with headache in children and adolescents?**

***This list includes also the international trial registries references that were excluded* *after assessing study inclusion/exclusion criteria.***

**A. From the list of eligible trials in the updated search (*n* = 90)**

**B. From the list of discarded trials in the updated search (*n* = 58)**

**A. From the list of eligible trials in the updated search**

**1. Abikoff2009**

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*Reason for exclusion: No usable safety data*

**2. Adler2008a, B4Z-MC-LYBV, NCT00190931**

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* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2002/21-411\_Strattera.cfm
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*Reason for exclusion: Adult participants*

**3. Adler2008b, NRP104.303, NCT00334880**

* Adler LA, Goodman DW, Kollins SH, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2008;69(9):1364-1373.
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*Reason for exclusion: Adult participants*

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*Reason for exclusion: Adult participants*

**5. Alder2009b, B4Z-US-LYCU, NCT00190736**

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*Reason for exclusion: Adult participants*

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* Additional data/information provided by Janssen

*Reason for exclusion: Adult participants*

**7. Adler2013, SPD489-403, NCT01101022**

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*Reason for exclusion: Adult participants*

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* Amiri S, Mohammadi MR, Mohammadi M, Nouroozinejad GH, Kahbazi M, Akhondzadeh S. Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(1):145-149.

*Reason for exclusion: Head to head study*

**9. Arnold2006**

* Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebocontrolled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry.* 2006;45(10):1196-1205.

*Reason for exclusion: Concomitant psychotropic medications allowed*

**10. Arnold2014, C1538/2027/AD/US, NCT00315276**

* Arnold VK, Feifel D, Earl CQ, Yang R, Adler LA. A 9-week, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study to evaluate the efficacy and safety of modafinil as treatment for adults with ADHD. *J Atten Disord.* 2014;18(2):133-144.
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*Reason for exclusion: Adult participants*

**11. Bain2013, NCT00429091**

* Bain E, Robieson W, Garimella T, Abi-Saab W, Apostol G, Saltarelli MD. A randomized, double-blind, placebocontrolled Phase 2 study of alpha4beta2 agonist ABT-894 in adults with ADHD. *Biochem Pharmacol.* 2011;82(8):1043.
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*Reason for exclusion: Adult participants*

**12. Bedard2015, NCT00183391**

* Bedard AC, Stein MA, Halperin JM, Krone B, Rajwan E, Newcorn JH. Differential impact of methylphenidate and atomoxetine on sustained attention in youth with attention-deficit/hyperactivity disorder. *J Child Psychol* *Psychiatry.* 2015;56(1):40-48.
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*Reason for exclusion: Head to head study*

**13. Biederman2006a, (subsample of NCT00181571)**

* Biederman J, Spencer T, Surman C, et al. A double-blind placebo-controlled randomized study of OROS methylphenidate in the treatment of adults with attention deficit hyperactivity disorder (ADHD): An interim analysis. *Biol Psychiatry.* 2005;57(8):106S-106S
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* Pooled in: Biederman J, Mick EO, Surman C, et al. Comparative acute efficacy and tolerability of OROS and immediate release formulations of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *BMC Psychiatry.* 2007;7:49.
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* Part of subjects from this study participated in: Bush G, Spencer TJ, Holmes J, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Arch Gen Psychiatry.* 2008;65(1):102-114

Note: Biederman2006a is a subsample of Biederman2010 (NCT00181571) (see list of excluded studies)

*Reason for exclusion: Adult participants*

**14. Biederman2012, 2008P000971, NCT00801229**

* Biederman J, Fried R, Hammerness P, et al. The effects of lisdexamfetamine dimesylate on the driving performance of young adults with ADHD: a randomized, double-blind, placebo-controlled study using a validated driving simulator paradigm. *J Psychiatr Res.* 2012;46(4):484-491.
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*Reason for exclusion: Adult participants*

**15. Biehl2016**

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*Reason for exclusion: Adult participants*

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*Reason for exclusion: Adult participants*

**17. Buitelaar1996**

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*Reason for exclusion: No number of participants with headaches (n) provided, only frequency of headaches in the article*

**18. Casas2013, EudraCT #: 2007-002111-82**

* Ramos-Quiroga JA, Kooij S, Trott GE, et al. Predictors of treatment outcome with long-acting methylphenidate in attention deficit hyperactivity disorder in adults. *Eur Neuropsychopharmacol*. 2009;19:S352-S3.
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* Casas M, Rosler M, Sandra Kooij JJ, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: a 13-week, randomized, double-blind, placebo-controlled, fixeddose study. *World J Biol Psychiatry.* 2013;14(4):268-281.
* Post hoc analysis in: Kooij JJ, Rosler M, Philipsen A, et al. Predictors and impact of non-adherence in adults with attention-deficit/hyperactivity disorder receiving OROS methylphenidate: results from a randomized, placebocontrolled trial. *BMC Psychiatry.* 2013;13:36.
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*Reason for exclusion: Adult participants*

**19. Casat1989**

* Casat CD, Pleasants DZ, Fleet JV. A double-blind trial of bupropion in children with attention-deficit disorder. *Psychopharmacol Bull.* 1987;23(1):120-122.
* Casat CD, Pleasants DZ, Schroeder DH, Parler DW. Bupropion in children with attention deficit disorder. *Psychopharmacol Bull.* 1989;25(2):198-201.

*Reason for exclusion: No usable safety data*

**20. Connor2000**

* Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clin Pediatr (Phila).* 2000;39(1):15-25.

*Reason for exclusion: Head to head study*

**21. Cook1993**

* Cook JR. The Effects of Methylphenidate on Resource Allocation in the Mental Processing of ADD Children [PhD thesis]. University of North Dakota, 1989.
* Cook JR, Mausbach T, Burd L, et al. A preliminary study of the relationship between central auditory processing disorder and attention deficit disorder. *J Psychiatry Neurosci.* 1993;18(3):130-137.

*Reason for exclusion: No usable safety data*

**22. Döpfner2003**

* Lehmkuhl G. Placebo-controlled, double-blind multicenter trial on the efficacy of sustained-release methylphenidate in children suffering from attention deficit hyperactivity disorder (ADHD), Phase III. Integrated Final Report. Institut für medizinische Informatik, *Biometrie und Epidemiologie, Universitätsklinikum Essen*, Trial no 6520-9979- 02, 1-9 2002
* Dopfner M, Banaschewski T, Schmidt J, et al. Langzeitwirksames Methylphenidat bei Kinderen mit Aufmerksamkeitsdefizit-Hyperaktivitatsstorungen-eine multizentrische Studie [Long-acting methylphenidate preparation in children with ADHD-a multicenter study]. Nervenheilkunde. 2003(2):85-92.
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*Reason for exclusion: No usable safety data*

**23. Durell2013, B4Z-US-LYDZ, NCT00510276**

* This study was presented in poster form at the Society of Biological Psychiatry 65th Annual Convention & Scientific Program, May 2010
* Altin M, Alev L, Durell TM, et al. Atomoxetine for the treatment of ADHD in young adults with an assessment of associated functional outcomes. *Klinik Psikofarmakoloji Bulteni.* 2011;21:S135-S136.
* Durell TM, Adler LA, Williams DW, et al. Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: a randomized, double-blind, placebo-controlled clinical trial. *J Clin Psychopharmacol.* 2013;33(1):45-54.
* Adler LA, Clemow DB, Williams DW, Durell TM. Atomoxetine effects on executive function as measured by the BRIEF--a in young adults with ADHD: a randomized, double-blind, placebo-controlled study. *PLoS ONE* *[Electronic Resource].* 2014;9(8):e104175.
* Addendum neurophysiological study (not pertinent for the present meta-analysis): Leuchter AF, McGough JJ, Korb AS, et al. Neurophysiologic predictors of response to atomoxetine in young adults with attention deficit hyperactivity disorder: a pilot project. *J Psychiatr Res.* 2014;54:11-18.
* https://clinicaltrials.gov/ct2/show/NCT00510276 (additional ID: B4Z-US-LYDZ)
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*Reason for exclusion: Adult participants*

**24. Efron1997**

* Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: A double-blind, crossover trial. *Pediatrics.* 1997;100(6):E6.
* Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics.* 1997;100(4):662-666.
* Efron D, Jarman FC, Barker MJ. Child and parent perceptions of stimulant medication treatment in attention deficit hyperactivity disorder. *J Paediatr Child Health.* 1998;34(3):288-292.
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*Reason for exclusion: Head to head study*

**25. Findling2008 , NCT00444574**

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* Faraone SV, Glatt SJ, Bukstein OG, Lopez FA, Arnold LE, Findling RL. Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. *J Atten Disord.* 2009;12(4):308-315.
* Extension study: Findling RL, Katic A, Rubin R, Moon E, Civil R, Li Y. A 6-month, open-label, extension study of the tolerability and effectiveness of the methylphenidate transdermal system in adolescents diagnosed with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2010;20(5):365-375. (NCT00501293)
* <https://clinicaltrials.gov/ct2/show/NCT00444574>

*Reason for exclusion: No number of participants with headaches (n) provided*

**26. Frick2017, SPD465-303, NCT00152022**

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*Reason for exclusion: Adult participants*

**27. Ginsberg2012, EUCTR2006-002553-80-SE**

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* https://clinicaltrials.gov/ct2/show/NCT00482313
* https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\_number:2006-002553-80
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*Reason for exclusion: Adult participants*

**28. Goodman2016, NCT00937040**

* Goodman DW, Starr HL, Ma YW, Rostain AL, Ascher S, Armstrong RB. Randomized, 6-Week, Placebo-Controlled Study of Treatment for Adult Attention-Deficit/Hyperactivity Disorder: Individualized Dosing of Osmotic-Release Oral System (OROS) Methylphenidate With a Goal of Symptom Remission. *J Clin* *Psychiatry.* 2017;78(1):105-114
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*Reason for exclusion: Adult participants*

**29. Goto2017, B4Z-JE-LYEE, NCT00962104**

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* Full CSR provided by Lilly

*Reason for exclusion: Adult participants*

**30. Grizenko2012**

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*Reason for exclusion: Cross-over without wash out*

**31. Herring2012, NCT00475735**

* Herring WJ, Adler LA, Baranak CC, Liu K, Snavely D, Michelson D. Effects of the histamine inverse agonist MK- 0249 in adult attention deficit disorder: A randomized, controlled, crossover study. *Biol Psychiatry.* 2010;1):217S.
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*Reason for exclusion: Adult participants*

**32. Huss2014 , CRIT124D2302, EUCTR2010-021533-31-DE, NCT01259492**

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* https://clinicaltrials.gov/ct2/show/NCT01259492
* https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\_number:2010-021533-31
* https://www.novctrd.com/CtrdWeb/displaypdf.nov?trialresultid=9544(study ID: CRIT124D2302)
* Additional information provided by Medice

*Reason for exclusion: Adult participants*

**33. Ivanov2020 (Conference proceedings. Includes change in ADHD ratings)**

* Ivanov I,Newcorn J, Krone B, et al. Neurobiological Basis of Reinforcement-Based Decision Making in Adults With ADHD Treated With Lisdexamfetamine Dimesylate. *Biological Psychiatry Supplement*. 2020: 87(9) S422-S423.

*Reason for exclusion: Adult participants*

**34. Iwanami2020**

* Iwanami, A., et al., Efficacy and Safety of Guanfacine Extended-Release in the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: Results of a Randomized, Double-Blind, Placebo-Controlled Study. *J Clin Psychiatry*, 2020. 81(3).

*Reasons for excludion: Adult participants*

**35. Jafarinia2012**

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*Reason for exclusion: Head to head study*

**36. Jain2011, NCT00556959**

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*Reason for exclusion: No number of participants with headaches (n) provided*

**37. Johnson2020**

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*Reasons for excludion: Not the medication of our interest*

**38, 39. Kay2009a,b**

* Kay GG, Michaels MA, Pakull B. Simulated driving changes in young adults with ADHD receiving mixed amphetamine salts extended release and atomoxetine. *J Atten Disord.* 2009;12(4):316-329. (These data were presented in part at the 158th Annual Meeting of the American Psychiatric Association in Atlanta, GA, on May 24, 2005
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*Note: cross-over with no wash out; only usable data: drop outs in pre cross-over phase*

*Reason for exclusion: Adult participants*

**40. Kooij2004**

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*Reason for exclusion: Adult participants*

**41. Kurlan2002**

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* Additional data provided by study author

*Reason for exclusion: No usable safety data*

**42. Lin2014, NCT00922636**

* Lin DY, Kratochvil CJ, Xu W, et al. A randomized trial of edivoxetine in pediatric patients with attentiondeficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2014;24(4):190-200.
* <https://clinicaltrials.gov/ct2/show/NCT00922636>

*Reason for exclusion: No pertinent ADHD medication in the present systematic review*

**43. Lin2016, NCT00917371**

* Lin HY, Gau SS. Atomoxetine Treatment Strengthens an Anti-Correlated Relationship between Functional Brain Networks in Medication-Naive Adults with Attention-Deficit Hyperactivity Disorder: A Randomized Double-Blind Placebo-Controlled Clinical Trial. *Int J Neuropsychopharmacol.* 2015;19(3).
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*Reason for exclusion: Adult participants*

**44. McCracken2016**

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* https://clinicaltrials.gov/ct2/show/NCT00429273

*Reason for exclusion: Head to head study*

**45. McRae-Clark2010, R21DA018221, NCT00360269**

* McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, White KG, Brady KT. A placebo-controlled trial of atomoxetine in marijuana-dependent individuals with attention deficit hyperactivity disorder. *Am J Addict.* 2010;19(6):481-489. (ID: R21DA018221).
* https://clinicaltrials.gov/ct2/show/NCT00360269
* Additional data from study author

*Reason for exclusion: Adult participants*

**46. Medori2008 , LAMDA-I EUCTR2004-000730-37, NCT00246220**

* Medori R, Kooij S, Ramos-Quiroga JA, Buitelaar J, Lee E, Casas M. Efficacy and safety of OROS methylphenidate in adults with ADHD the long-acting methylphenidate in adult ADHD (LAMDA) trial. *J Neural Transm (Vienna).* 2007; 114(7).
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*Reason for exclusion: Adult participants*

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*Reason for exclusion: Adult participants*

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*Reason for exclusion: Head to head study*

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*Reason for exclusion: No number of participants with headaches (n) provided*

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*Reason for exclusion: Adult participants*

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* Note: Full study protocol in supplemental material of Schrantee et al. JAMA Psychiatry 2016
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*Reason for exclusion: Adult participants*

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*Reason for exclusion: Cross-over without wash out*

**70. Sutherland2012, NCT00174226**

* Sutherland SM, Adler LA, Chen C, Smith MD, Feltner DE. An 8-week, randomized controlled trial of atomoxetine, atomoxetine plus buspirone, or placebo in adults with ADHD. *J Clin Psychiatry.* 2012;73(4):445-450.
* <https://clinicaltrials.gov/ct2/show/NCT00174226>

*Reason for exclusion: Adult participants*

**71. Takahashi2014, NCT01323192**

* Takahashi N, Koh T, Tominaga Y, Saito Y, Kashimoto Y, Matsumura T. A randomized, double-blind, placebocontrolled, parallel-group study to evaluate the efficacy and safety of osmotic-controlled release oral delivery system methylphenidate HCl in adults with attention-deficit/hyperactivity disorder in Japan. *World J Biol* *Psychiatry.* 2014.
* https://clinicaltrials.gov/ct2/show/NCT01323192
* <https://yoda.yale.edu/sites/default/files/nct01323192.pdf>

*Reason for exclusion: Adult participants*

**72. Taylor1987**

* Taylor E, Schachar R, Thorley G, Wieselberg HM, Everitt B, Rutter M. Which boys respond to stimulant medication? A controlled trial of methylphenidate in boys with disruptive behaviour. *Psychol Med.* 1987;17(1):121-143.
* Schachar R, Taylor E, Wieselberg M, Thorley G, Rutter M. Changes in family function and relationships in children who respond to methylphenidate. *J Am Acad Child Adolesc Psychiatry.* 1987;26(5):728-732.

*Reason for exclusion: No number of participants with headaches (n) provided*

**73. Taylor2000**

* Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol.* 2000;10(4):311-320.
* Taylor IF. Comparing modafinil to dextroamphetamine in the treatment of adult adhd. *153rd Annual Meeting of the American Psychiatric Association.* 2000.
* Taylor FB. Comparing modafinil to dextroamphetamine in the treatment of adult adhd. *155th Annual Meeting of the American Psychiatric Association.* 2002.

*Reason for exclusion: Adult participants*

**74. Taylor2001**

* Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attentiondeficit/hyperactivity disorder. *J Clin Psychopharmacol.* 2001;21(2):223-228. Taylor IF. Comparing guanfacine and dextroamphetamine for adult adhd: efficacy and implications. *153rd Annual Meeting of the American Psychiatric Association.* 2000.
* Taylor FB. Comparing guanfacine and dextroamphetamine for adult adhd: efficacy and implications. 155th Annual Meeting of the American Psychiatric Association 2002

*Reason for exclusion: Adult participants*

**75. van der Meere1999**

* van der Meere J, Gunning B, Stemerdink N. The effect of methylphenidate and clonidine on response inhibition and state regulation in children with ADHD. *J Child Psychol Psychiatry.* 1999;40(2):291-298.
* Gunning WB. A Controlled Trial of Clonidine in Hyperkinetic Children. Erasmus Universiteit Rotterdam, 1992. <http://repub.eur.nl/res/pub/8339/920311_Gunning,%20Willem%20Boudewijn.pdf>

*Reason for exclusion: No number of participants with headaches (n) provided*

**76. Wang2007, NCT00486083, B4Z-MC-LYBR (6934)**

* Levine L, Wang Y, Zheng Y, Du Y, Cho SC, Gao H, Marquez-Caraveo ME, Rogers AK, Williams DW. Atomoxetine vs. methylphenidate in ADHD treatment: an international pediatric trials. *Eur Neuropsychopharamacol* 2005, 15, Suppl 3, S602.
* Wang Y, Zheng Y, Du Y, et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. *The Aust N Z J Psychiatry.* 2007;41(3):222-230.
* https://clinicaltrials.gov/ct2/show/NCT00486083
* https://assets.contentful.com/hadumfdtzsru/4RGQpHv0BOWMMcCcAyii2s/a91d17111b5aa1326bef55e28cf7cc06/Atomoxetine-B4Z-MC-LYBR.pdf
* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2002/21-411\_Strattera.cfm

*Reason for exclusion: Head to head study*

**77. Weisler2006, SLI381-303**

* Weisler RH, Biederman J, Chrisman AK, Timothy TP, Frazer N, Tulloch SJ. Long-Term Safety and Efficacy of Once-Daily Adderall Extended Release in Adults With ADHD. 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA2003:Nr647.
* Weisler RH, Chrisman AK, Wilens TE. Adderall xr dosed once daily in adult patients with adhd. 156th *Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA. 2003:No. 33*.http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/838/CN-00592838/frame.html.
* Long-term follow-up in: Biederman J, Spencer TJ, Wilens TE, Weisler RH, Read SC, Tulloch SJ. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr.* 2005;10(12 Suppl 20):16-25.
* Weisler RH, Biederman J, Spencer TJ, Wilens TE. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr.* 2005;10(12 Suppl 20):35-43.
* Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr.* 2006;11(8):625-639.
* Pooled in: Lasser R, Dirks B, Adeyi B, Babcock T. Comparative efficacy and safety of lisdexamfetamine dimesylate and mixed amphetamine salts extended release in adults with attention-deficit/hyperactivity disorder. *Prim* *psychiatry.* 2010;17(9):44-54.
* Additional data provided by Shire (ID: SLI381-303)

*Reason for exclusion: Adult participants*

**78. Weisler2012, NCT00880217**

* Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C, Investigato ATTS. Randomized Clinical Study of a Histamine H-3 Receptor Antagonist for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder. *CNS* *Drugs*. 2012;26(5):421-434.
* https://clinicaltrials.gov/ct2/show/NCT00880217 (additional ID: 31001074-ATT2001**)**
* Additional information from manufacturer

*Reason for exclusion: Adult participants*

**79. Weisler2017, NCT02604407**

* Weisler RH, Greenbaum M, Arnold V, Yu M, Yan B, Jaffee M, Robertson B. Efficacy and Safety of SHP465 Mixed Amphetamine Salts in the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: Results of a Randomized, Double-Blind, Placebo-Controlled, Forced-Dose Clinical Study. CNS Drugs. 2017;31(8):685-697.
* <https://clinicaltrials.gov/ct2/show/NCT02604407>

*Reason for exclusion: Adult participants*

**80. Weiss2005, B4Z-MC-LYAW**

* Weiss M, Tannock R, Kratochvil C, et al. Placebo-controlled study of once-daily atomoxetine in the school setting. *Eur Neuropsychopharmacol.* 2003;13(Supplement 4):S456-S457.
* Pooled in: Perwien AR, Faries DE, Kratochvil CJ, Sumner CR, Kelsey DK, Allen AJ. Improvement in health-related quality of life in children with ADHD: an analysis of placebo controlled studies of atomoxetine. *J Dev Behav* *Pediatr.* 2004;25(4):264-271.
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* Bohnstedt BN, Kronenberger WG, Dunn DW, et al. Investigator ratings of ADHD symptoms during a randomized, placebo-controlled trial of atomoxetine: a comparison of parents and teachers as informants. *J Atten Disord.* 2005;8(4):153-159.
* Brown RT, Perwien A, Faries DE, Kratochvil CJ, Vaughan BS. Atomoxetine in the management of children with ADHD: effects on quality of life and school functioning. *Clin Pediatr (Phila).* 2006;45(9):819-827.
* Commentary: Barton J. Atomoxetine improves teacher rated symptoms in children with ADHD more than placebo. *Evid Based Ment Health.* 2006;9(1):7.
* Pooled in: Biederman J, Gao H, Rogers AK, Spencer TJ. Comparison of parent and teacher reports of attentiondeficit/hyperactivity disorder symptoms from two placebo‐controlled studies of atomoxetine in children. *Biol* *Psychiatry.* 2006;60(10):1106‐1110.
* Pooled in: Biederman J, Spencer TJ, Newcorn JH, et al. Effect of comorbid symptoms of oppositional defiant disorder on responses to atomoxetine in children with ADHD: a meta-analysis of controlled clinical trial data. *Psychopharmacology (Berl).* 2007;190:31-41
* Related to previous reference: Biederman J, Spencer T, Newcorn J, Gao H, Milton D, Feldman P. Does the Presence of Comorbid ODD Affect Responses to Atomoxetine? 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA2005.
* https://assets.contentful.com/hadumfdtzsru/1PT69wZkT2UosACGuAImuw/f80b9521e50d1cb2dce4fcd31c96d845/Atomoxetine-B4Z-MC-LYAW\_a\_.pdf
* https://assets.contentful.com/hadumfdtzsru/28G1mHvyIkSqww8w4AueWU/e99d85ebd3c15c789c20791f3d52410f/Atomoxetine-B4Z-MC-LYAW\_b\_.pdf
* https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2002/21-411\_Strattera.cfm

*Reason for exclusion: No number of participants with headaches (n) provided*

**81. Weiss 2020**

* Weiss M, Childress AC, Donnelly GAE. Efficacy and safety of PRC-063, extended release multilayer methylphenidate in adults with ADHD including 6-month open-label extension. *J Attention Disorders*. 2020:

*Reasons for excludion: Adult participants*

**82. Wender2011**

* Wender PH, Reimherr FW, Marchant B, Czajkowski L, Sanford ME. A placebo-controlled, long-term trial of methylphenidate in the treatment of adults with ADHD. *2001 Annual Meeting of the American Psychiatric* *Association.* 2001.
* Wender Paul H. A placebo-controlled, long-term trial of methylphenidate in the treatment of adults with adhd. *155th Annual Meeting of the American Psychiatric Association 2002.*
* Wender PH, Szajkowski L, Marchant B, Reimherr FW, Sanford E, Eden J. A Long-Term Study of Methylphenidate in the Treatment of ADHD in Adults. *156th Annual Meeting of the American Psychiatric Association, May 17-22,* *San Francisco CA2003:Nr708.*
* Wender PH, Reimherr FW, Marchant B, Sanford E, Czajkowski L. A Long-Term Trial of Methylphenidate in the Treatment of ADHD in Adults. 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA. 2003:Nr709.
* Wender PH, Reimherr FW, Marchant BK, Sanford ME, Czajkowski LA, Tomb DA. A one year trial of methylphenidate in the treatment of ADHD. *J Atten Disord.* 2011;15(1):36-45.
* https://clinicaltrials.gov/ct2/show/NCT00693212
* Additional data from study author

*Reason for exclusion: Adult participants*

**83. Wilens2001**

* Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry.* 2001;158(2):282-288.
* Commentary in: Ferre, J.C. & Nutt, D. (2001). Bupropion improved symptoms in adults with attention deficit hyperactivity disorder. Evidence Based Mental Health, 158, 282-288
* Commentary in: Newcorn JH. Bupropion for adults with attention deficit hyperactivity disorder. *Curr Psychiatry Rep.* 2002;4(2):86-87.
* Post hoc analysis in: Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2005;66(2):253-259.

*Reason for exclusion: Adult participants*

**84. Wilens2005, NCT00048360**

* Wilens TE, Hudziak JJ, Connor DF, et al. A Controlled Trial of Extended-Release Bupropion in Adult ADHD. *157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, NY2004:Nr576*.
* Wilens TE, Haight BR, Horrigan JP, et al. Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. *Biol Psychiatry.* 2005;57(7):793-801.
* https://clinicaltrials.gov/ct2/show/NCT00048360 (other ID: AK130934)

*Reason for exclusion: Adult participants*

**85. Wilens2008, B4Z-MC-LYBY, NCT00190957**

* Wilens TE, Adler LA, Weiss MD, Ramsey JL, Moore RF, Renard D, Trzepacz PT, Schuh LM, Dittmann RW, Levine LR, No. Atomoxetine treatment of adults with ADHD and comorbid alcohol abuse disorder. *Pharmacopsychiatry*. 2007; 40: 150
* Wilens TE, Adler LA, Weiss MD, et al. Atomoxetine treatment of adults with ADHD and comorbid alcohol abuse*. Proceedings of the 69th Annual Scientific Meeting of the College on Problems of Drug Dependence; 2007 June 16-21; Quebec City, Canada. 2007*.
* Wilens TE, Adler LA, Weiss MD, et al. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. *Drug Alcohol Depend.* 2008;96(1-2):145-154.
* Pooled in: Adler L, Wilens T, Zhang S, et al. Retrospective safety analysis of atomoxetine in adult ADHD patients with or without comorbid alcohol abuse and dependence. *Am J Addict.* 2009;18(5):393-401
* Pooled in: Reimherr FW, Olsen J, Marchant BK, et al. ADHD Symptoms Associated with Comorbid Alcohol Dependence Or Abuse: Comparison of Subject Attributes within ADHD Clinical Trials*. Biol Psychiatry*. 2009;65:116S.
* Post hoc analysis in: Wilens TE, Adler LA, Tanaka Y, et al. Correlates of alcohol use in adults with ADHD and comorbid alcohol use disorders: exploratory analysis of a placebo-controlled trial of atomoxetine. *Curr Med Res* *Opin.* 2011;27(12):2309-2320.
* https://clinicaltrials.gov/ct2/show/NCT00190957
* https://assets.contentful.com/hadumfdtzsru/1PXcFgjDCAW6EUOYMg4I80/da1e7c4d91490b68c9fd23385bdc3920/Atomoxetine-B4Z-MC-LYBY.pdf
* Full CSR provided by Lilly

*Reason for exclusion: Adult participants*

**86. Wietecha2013, NCT00607919**

* Shaywitz SE, Shaywitz BA, Wietecha LA, et al. Effects of atomoxetine on reading abilities in children with dyslexia and children with attention deficit/hyperactivity disorder and comorbid dyslexia. *Ann Neurol.* 2012;72:S204.
* Wietecha L, Williams D, Shaywitz S, et al. Atomoxetine improved attention in children and adolescents with attention-deficit/hyperactivity disorder and dyslexia in a 16 week, acute, randomized, double-blind trial. *J Child* *Adolesc Psychopharmacol.* 2013;23(9):605-613.
* Post-hoc analysis in: McBurnett K, Clemow D, Williams D, Villodas M, Wietecha L, Barkley R. Atomoxetine- Related Change in Sluggish Cognitive Tempo Is Partially Independent of Change in Attention-Deficit/Hyperactivity Disorder Inattentive Symptoms. *J Child Adolesc Psychopharmacol.* 2016;27:38-42.
* Shaywitz S, Shaywitz B, Wietecha L, et al. Effect of Atomoxetine Treatment on Reading and Phonological Skills in Children with Dyslexia or Attention-Deficit/Hyperactivity Disorder and Comorbid Dyslexia in a Randomized, Placebo-Controlled Trial. *J Child Adolesc Psychopharmacol.* 2016;27(1):19-28.
* https://clinicaltrials.gov/ct2/show/NCT00607919

*Reason for exclusion: Safety data including participants without ADHD diagnosis*

**87. Wigal 2005, SLI381-404, NCT00506727**

* Wigal S, McGough JJ, Posner K, Kollins SH, Michaels A, Tulloch SJ. Analog classroom study of amphetamine extended release and atomoxetine in youth with ADHD. *157th Annual Meeting of the American Psychiatric* *Association; 2004 May 1-6; New York, NY.* 2004.
* Wigal SB, McGough JJ, McCracken JT, et al. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J Atten Disord.* 2005;9(1):275-289.
* Data on girls only in: Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. Clin Ther. Feb 2006;28(2):280-293.
* Post hoc analysis in: Faraone SV, Wigal SB, Hodgkins P. Forecasting three-month outcomes in a laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with ADHD. *J Atten Disord.* 2007;11(1):74-82.
* https://clinicaltrials.gov/ct2/show/NCT00506727 (other ID: SLI381-404**)**

*Reason for exclusion: Head to head study*

**88. Wilens2011, NCT00528697**

* Wilens TE, Gault LM, Childress A, et al. Safety and efficacy of ABT-089 in pediatric attention-deficit/hyperactivity disorder: results from two randomized placebo-controlled clinical trials. *J Am Acad Child Adolesc Psychiatry.* 2011;50(1):73-84 e71
* <https://clinicaltrials.gov/ct2/show/NCT00528697>

*Reason for exclusion: No pertinent ADHD medication in the present systematic review*

**89. Winhusen2010, NCT00253747**

* Winhusen TM, Somoza EC, Brigham GS, et al. Impact of attention-deficit/hyperactivity disorder (ADHD) treatment on smoking cessation intervention in ADHD smokers: a randomized, double-blind, placebo-controlled trial. *J Clin* *Psychiatry.* 2010;71(12):1680-1688.
* Covey LS, Hu MC, Winhusen T, Weissman J, Berlin I, Nunes EV. OROS-methylphenidate or placebo for adult smokers with attention deficit hyperactivity disorder: racial/ethnic differences. *Drug Alcohol Depend.* 2010;110(1-2):156-159.
* Covey LS, Hu MC, Weissman J, Croghan I, Adler L, Winhusen T. Divergence by ADHD subtype in smoking cessation response to OROS-methylphenidate. *Nicotine Tob Res.* 2011;13(10):1003-1008.
* Luo SX, Wall M, Covey L, Hu MC, Scodes JM, Levin FR, Nunes EV, Winhusen T. Exploring longitudinal course and treatment-baseline severity interactions in secondary outcomes of smoking cessation treatment in individuals with attention-deficit hyperactivity disorder. Am J Drug Alcohol Abuse. 2018;44(6):653-659.
* Pooled in: Winhusen TM, Lewis DF, Riggs PD, et al. Subjective effects, misuse, and adverse effects of osmoticrelease methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder. *J* *Child Adolesc Psychopharmacol.* 2011;21(5):455-463.
* Berlin I, Hu MC, Covey LS, Winhusen T. Attention-deficit/hyperactivity disorder (ADHD) symptoms, craving to smoke, and tobacco withdrawal symptoms in adult smokers with ADHD. *Drug Alcohol Depend.* 2012;124(3):268-273.
* Westover AN, Nakonezny PA, Winhusen T, Adinoff B, Vongpatanasin W. Risk of methylphenidate-induced prehypertension in normotensive adult smokers with attention deficit hyperactivity disorder. *J Clin Hypertens* *(Greenwich, Conn.).* 2013;15(2):124-132.
* Post hoc analysis in: Nunes EV, Covey LS, Brigham G, et al. Treating nicotine dependence by targeting attentiondeficit/hyperactivity disorder (ADHD) with OROS methylphenidate: the role of baseline ADHD severity and treatment response. *J Clin Psychiatry.* 2013;74(10):983-990.
* Post hoc analysis in: Heffner JL, Lewis DF, Winhusen TM. Osmotic release oral system methylphenidate prevents weight gain during a smoking-cessation attempt in adults with ADHD. *Nicotine Tob Res: official journal of the* *Society for Research on Nicotine and Tobacco.* 2013;15(2):583-587.
* Post hoc analysis in: Heffner JL, Lewis DF, Winhusen TM. Preliminary evidence that adherence to counseling mediates the effects of pretreatment self-efficacy and motivation on outcome of a cessation attempt in smokers with ADHD. *Nicotine Tob Res: official journal of the Society for Research on Nicotine and Tobacco.* 2013;15(2):393-400.
* Secondary analysis in: Luo, S.X., Covey, L., Hu, M.C., Levin, F.R., & Nunes, E.V. (2013). Predictive modeling and nonlinear treatment effects in a multicenter, randomized controlled trial of methylphenidate in smoke cessation intervention. *Am J Addict*. 22 (3), 305.
* Secondary analysis in: Luo SX, Covey LS, Hu MC, Levin FR, Nunes EV, Winhusen TM. Toward personalized smoking-cessation treatment: Using a predictive modeling approach to guide decisions regarding stimulant medication treatment of attention-deficit/hyperactivity disorder (ADHD) in smokers. *Am J Addict.* 2015;24(4):348-356.
* Luo SX, Wall MM, Covey LS, et al. Modeling potential mechanisms of differential treatment effects in osmoticrelease methylphenidate for smoking cessation. *Drug Alcohol Depend.* 2015;146:e188.
* https://clinicaltrials.gov/ct2/show/NCT00253747
* Additional information from study authors

*Reason for exclusion: Adult participants*

**90. Young2011, B4Z-US-LYCW, NCT00190775**

* Young JL, Sarkis E, Qiao M, Wietecha L. Once-daily treatment with atomoxetine in adults with attentiondeficit/hyperactivity disorder: a 24-week, randomized, double-blind, placebo-controlled trial. *Clin Neuropharmacol.* 2011;34(2):51-60.
* Pooled in: Wietecha L, Young J, Ruff D, Dunn D, Findling RL, Saylor K. Atomoxetine once daily for 24 weeks in adults with attention-deficit/hyperactivity disorder (ADHD): impact of treatment on family functioning. *Clin Neuropharmacol.* 2012;35(3):125-133.
* Wietecha LA, Clemow DB, Buchanan AS, Young JL, Sarkis EH, Findling RL. Atomoxetine Increased Effect over Time in Adults with Attention-Deficit/Hyperactivity Disorder Treated for up to 6 Months: Pooled Analysis of Two Double-Blind, Placebo-Controlled, Randomized Trials. *CNS Neurosci Ther.* 2016;22(7):546-557.
* https://clinicaltrials.gov/ct2/show/NCT00190775 (other ID: B4Z-US-LYCW(9043)
* Full CSR provided by Lilly

*Reason for exclusion: Adult participants*

**B. From the list of discarded trials in the updated search**

1. **Aharonovich2006**

* Aharonovich E, Garawi F, Bisaga A, et al. Concurrent cannabis use during treatment for comorbid ADHD and cocaine dependence: effects on outcome. *Am J Drug Alcohol Abuse.* 2006;32(4):629-635.

*Reason for exclusion: Concurrent CBT Adult participants*

1. **Altszuler2017**

* Altszuler AR, Morrow AS, Merrill BM, et al. The Effects of Stimulant Medication and Training on Sports Competence Among Children With ADHD. *J Clin Child Adolesc Psychol.* 2017:1-13.

*Reason for exclusion: No outcomes of interest; concomitant sport training*

*No safety data*

1. **Beery2013**

* Beery SH, Quay HC, Pelham WE, Jr. Differential Response to Methylphenidate in Inattentive and Combined Subtype ADHD. *J Atten Disord.* 2017;21(1):62-7

*Reason for exclusion: Concomitant behavioural treatment No safety data*

1. **Borcherding1989**

* Borcherding BG, Keysor CS, Cooper TB, Rapoport JL. Differential effects of methylphenidate and dextroamphetamine on the motor activity level of hyperactive children. *Neuropsychopharmacology.* 1989;2(4):255-263.
* Elia J, Borcherding BG, Potter WZ, Mefford IN, Rapoport JL, Keysor CS. Stimulant drug treatment of hyperactivity: biochemical correlates. *Clin Pharmacol Ther*. 1990;48(1):57-66
* Borcherding BG, Keysor CS, Rapoport JL, Elia J, Amass J. Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability? *Psychiatry Res.*1990;33(1):83-94
* Sharp WS,Walter JM,MarshWL, Ritchie GF,HamburgerSD, Elia J, Borcherding BG, Potter WZ, Mefford IN, Rapoport JL, Keysor CS. Stimulant drug treatment of hyperactivity: biochemical correlates. *Clin PharmacolTher.* 1990;48(1):57-66.
* Elia J, Borcherding BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? *Psychiatry Res.* 1991;36(2):141-155.
* Elia J, Welsh PA, Gullotta CS, Rapoport JL. Classroom academic performance: improvement with both methylphenidate and dextroamphetamine in ADHD boys. *J Child Psychol Psychiatry.* 1993;34(5):785-804.
* Schmidt ME, Kruesi MJ, Elia J, et al. Effect of dextroamphetamine and methylphenidate on calcium and magnesium concentration in hyperactive boys. *Psychiatry Res.* 1994;54(2):199-210
* Castellanos FX, Elia J, Kruesi MJP, et al. Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit hyperactivity disorder. *Neuropsychopharmacology.* 1996;14(2):125-137.
* Castellanos FX, Giedd JN, Elia J, et al. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry.* 1997;36(5):589-596.
* Castellanos FX. ADHD in girls: clinical comparability of a research sample. *J Am Acad Child Adolesc Psychiatry.* 1999;38(1):40–7

*Reason for exclusion: Co-treatment (therapeutic art) No safety data*

1. **Borden1989**

* Borden KA, Brown RT. Attributional outcomes: The subtle messages of treatments for attention deficit disorder. *Cognit Ther Res*. 1989(2):147-160.

*Reason for exclusion: No arms of interest for the present meta-analysis (cognitive training, methylphenidate+cognitive training, cognitive training + placebo) No safety data*

1. **Brown1985c**

* Brown RT, Wynne ME, Medenis R. Methylphenidate and cognitive therapy: A comparison of treatment approaches with hyperactive boys. *J Abnorm Child Psychol.* 1985(1):69-87.

*Reason for exclusion: No arms of interest for the present meta-analysis (methylphenidate, cognitive training, cognitive training plus methylphenidate, no treatment) No safety data*

1. **Brown1986a**

* Brown RT, Borden KA, Wynne ME, Schleser R, Clingerman SR. Methylphenidate and cognitive therapy with ADD children: a methodological reconsideration. *J Abnorm Child Psychol.* 1986;14(4):481-497.

*Reason for exclusion: No arms of interests for the present meta-analysis: methylphenidate, cognitive training, cognitive training plus methylphenidate, no treatment No safety data*

1. **Brown1986b**

* Brown RT, Wynne ME, Borden KA, Clingerman SR, Geniesse R, Spunt AL. Methylphenidate and cognitive therapy in children with attention deficit disorder: a double-blind trial. *J Dev Behav Pediatr.* 1986;7(3):163-174.

*Reason for exclusion: not appropriate design No safety data*

1. **Brown1987**

* Brown RT, Borden KA, Wynne ME. Compliance with pharmacological and cognitive treatments for attention deficit

disorder. *J Am Acad Child Adolesc Psychiatry.* 1987;26(4):521-526.

*Reason for exclusion: Concurrent additional treatments No safety data*

1. **Brown1988a**

* Brown RT, Borden KA, Wynne ME, Spunt AL, Clingerman SR. Patterns of compliance in a treatment program for children with attention deficit disorder. *J. Compliance Health Care.* 1988(1):23-39.

*Reason for exclusion: No pertinent arms for the present meta-analysis ((1) cognitive therapy plus placebo, (2) cognitive therapy plus methylphenidate, (3) methylphenidate plus attention control, or (4) placebo plus attention control) No safety data*

1. **Bukstein1998**

* Bukstein OG, Kolko DJ. Effects of methylphenidate on aggressive urban children with attention deficit hyperactivity disorder. *J Clin Child Psychol.* 1998;27(3):340-351.

*Reason for exclusion: Additional behavioral treatment component No cases (n) of side effects provided*

1. **Carpentier2005**

* Carpentier PJ, de Jong CA, Dijkstra BA, Verbrugge CA, Krabbe PF. A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. *Addiction.* 2005;100(12):1868-1874.

*Reason for exclusion: Co-treatment during trial Adult participants*

1. **Conners1996a**

* Conners CK, Levin ED, Sparrow E, et al. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). *Psychopharmacol Bull.* 1996;32(1):67-73.

*Reason for exclusion: Transdermal formulations Adult participants*

1. **Corkum 2020**

* Corkum P, Begum EA, Rusak B, et al. The Effects of Extended-Release Stimulant Medication on Sleep in Children with ADHD. J Can Acad Child Adolesc Psychiatry. 2020;29:33-43.

*Reason for exclusion: no outome of interest No outcome of interest*

1. **CTRI/2017/01/007665**

* http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=14324

*Reasons for exclusion: Atomoxetine vs psychological intervention vs combination Not RCT*

1. **Diamond1999**

* Diamond IR, Tannock R, Schachar RJ. Response to methylphenidate in children with ADHD and comorbid anxiety. *J Am Acad Child Adolesc Psychiatry.* 1999;38(4):402-409.

*Reason for exclusion: Co-intervention No useful data for headache measurement*

1. **Döpfner2004b**

* Dopfner M, Breuer D, Schurmann S, Metternich TW, Rademacher C, Lehmkuhl G. Effectiveness of an adaptive multimodal treatment in children with Attention-Deficit Hyperactivity Disorder - Global outcome. *Eur Child* *Adolesc Psychiatry, Supplement.* 2004;13(1):I/117-I/129.

*Reason for exclusion: No arms of interest for the present meta-analysis (methylphenidate + behavioural training vs.behavioural training No safety data*

1. **Duric2012**

* Duric NS, Assmus J, Gundersen D, Elgen IB. Neurofeedback for the treatment of children and adolescents with ADHD: a randomized and controlled clinical trial using parental reports. *BMC Psychiatry.* 2012;12:107.

*Reason for exclusion: No arms of interest for the present meta-analysis (methylphenidate, neurofeedback, methylphenidate +neurofeedback) No safety data*

1. **EUCTR2010-019981-94-FI**

* https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\_number:2010-019981-94

*Reasons for exclusion: Co-treatment Adult participants*

1. **Findling2001**

* Findling RL, Short EJ, Manos MJ. Short-term cardiovascular effects of methylphenidate and adderall. *J Am Acad Child Adolesc Psychiatry.* 2001;40(5):525-529.

*Reason for exclusion: Clinician blinded to dose but not identity of the medication*

*Head to head study*

1. **Firestone1981**

* Firestone P. Differential Effects of Parent Training and Stimulant Medication with Hyperactives: A Progress Report. *Children's Hospital of Eastern Ontario, Ottawa (Canada). 1979.*
* Firestone P, Kelly MJ, Goodman JT, Davey J. Differential effects of parent training and stimulant medication with hyperactives: a progress report. *J Am Acad Child Psychiatr*. 1981;20(1): 135–47.

*Reason for exclusion: No appropriate arms for the present meta-analysis No safety data*

1. **Firestone1986**

* Firestone P, Crowe D, Goodman JT, McGrath P. Vicissitudes of follow-up studies: differential effects of parent training and stimulant medication with hyperactives. *Am J Orthopsychiatry.* 1986;56(2):184-194.

*Reason for exclusion: Study arms (parent training +medication; parent training plus placebo; medicatin only) not appropriate for the present meta-analysis No safety data*

1. **Gittelman-Klein1976b**

* Gittelman-Klein R, Klein DF, Abikoff H, Katz S, Gloisten AC, Kates W. Relative efficacy of methylphenidate and behavior modification in hyperkinetic children: an interim report. *J Abnorm Child Psychol.* 1976;4(4):361-379.

*Reason for exclusion: No study arms of interest for the present meta-analysis No safety data*

1. **Granger1996**

* Granger DA, Whalen CK, Henker B, et al. ADHD boys' behavior during structured classroom social activities: Effects of social demands, teacher proximity, and methylphenidate. *J Atten Disord.* 1996;1(1): 16-30.

*Reason for exclusion: Co-intervention No safety data*

1. **Hinshaw1989a**

* Hinshaw SP, Henker B, Whalen CK, Erhardt D, Dunnington RE, Jr. Aggressive, prosocial, and nonsocial behavior in hyperactive boys: dose effects of methylphenidate in naturalistic settings. *J Consult Clin Psychol.* 1989;57(5):636-643.

*Reason for exclusion: Co-treatment Cross-over without wash out.*

1. **ISRCTN52376787**

* http://isrctn.com/ISRCTN52376787

*Reasons for exclusion: Methylphenidate vs. no methylphenidate No safety data provided*

1. **James2001**

* James RS, Walter JM, Sharp WS, Castellanos FX. Comparative efficacy of 3 amphetamine preparations in children with adhd. *39th Annual Meeting of the American College of* Neuropsychopharmacology*. 2000; Dec 10-14; San Juan, Puerto Rico.* 2000.
* James RS, Sharp WS, Bastain TM, et al. Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *J Am Acad Child Adolesc Psychiatry.* 2001;40(11):1268-1276.

*Reason for exclusion: Co-treatment (behavior management techniques used during the programme) No number of headache cases (n) provided*

1. **Klein1997b**

* Klein RG, Abikoff H. Behavior therapy and methylphenidate in the treatment of children with ADHD. *J Atten Disord.* 1997;2(2):89-114.

*Reason for exclusion: No arms of interest for the present meta-analysis (Stimulants, parent and teacher training, stimulants+ parent and teacher training) No safety data*

1. **Konstenius2010**

* Konstenius M, Jayaram-Lindstrom N, Beck O, Franck J. Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: a pilot study. *Drug Alcohol Depend.* 2010;108(1-2):130-133.
* Konstenius M, Jayaram N, Guterstam J, Franck J. Pharmacological treatment of ADHD with amphetamine dependence. *Acta Neuropsychiatr.* 2013;25(S1): 13-14.

*Reason for exclusion: Co-treatment: skills training programme Adult participants*

1. **Kratochvil2011 (NCT00254462; K23MH066127)**

* Kratochvil CJ, Vaughan BS, Stoner JA, et al. A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. *Pediatrics.* 2011;127(4):e862-868.
* https://clinicaltrials.gov/ct2/show/NCT00254462

*Reason for exclusion: Co-treatment with behavioral strategies No number of headache cases (n) provided*

1. **Levin1998**

* Levin FR, Evans SM, McDowell DM, Kleber HD. Methylphenidate treatment for cocaine abusers with adult attention-deficit/hyperactivity disorder: a pilot study. *J Clin Psychiatry.* 1998;59(6):300-305.
* Levin FR, Evans SM, Kleber HD. Methylphenidate Treatment for Cocaine Abusers with Adult Attention-Defict/Hyperactivity Disorder. *NIDA Res Monogr.* 1999:39.

*Reason for exclusion: Co-treatment with psychotherapy Adult participants*

1. **Levin2001**

* Levin ED, Conners CK, Silva D, Canu W, March J. Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder. *Exp Clin Psychopharmacol.* 2001;9(1):83-90.

*Reason for exclusion: No outcomes and no arms of interest for the present meta-analysis (placebo patch + placebo pill (control), nicotine patch + placebo pill (nicotine), placebo patch + methylphenidate pill (methylphenidate), and nicotine patch + methylphenidate pill (nicotine + methylphenidate) Adult participants*

1. **Levin2006 (NCT00061087)**

* Levin FR, Evans SM, Brooks D, Sullivan M, Nunes E, Vosburg S. Treatment of adult ADHD in methadone maintenance patients: Preliminary findings from a double-blind, three-armed, placebo-controlled trial. *Drug Alcohol* *Depend.* 2002;66:S102.
* Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. *Drug Alcohol Depend.* 2006;81(2):137-148.
* https://clinicaltrials.gov/ct2/show/NCT00061087

*Reason for exclusion*: *Co-treatment Adult participants*

1. **Levin2007 (NCT00136734)**

* Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. *Drug Alcohol Depend.* 2007;87(1):20-29.
* https://clinicaltrials.gov/ct2/show/NCT00136734

*Reason for exclusion: Co-treatment with cognitive therapy Adult participants*

1. **Levin2015 (NCT00553319)**

* Levin FR, Mariani JJ, Specker S, et al. Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2015;72(6):593-602.
* Levin FR, Mariani JJ, Mahony A, et al. Mixed amphetamine salts-extended release for ADHD adults with cocaine use disorder. *Drug Alcohol Depend.* 2015;146:e175.
* Notzon D, Mariani JJ, Pavlicova M, et al. Mixed-amphetamine salts increase abstinence from marijuana in patients with co-occurring attention-deficit/hyperactivity disorder and cocaine dependence. Drug *Alcohol Depend.* 2015;156:e164.
* Notzon DP, Mariani JJ, Pavlicova M, Glass A, Mahony AL, Brooks DJ, Grabowski J, Levin FR. Mixedamphetamine salts increase abstinence from marijuana in patients with co-occurring attention-deficit/hyperactivity disorder and cocaine dependence. *Am J Addict*. 2016;25(8):666-672
* https://clinicaltrials.gov/ct2/show/NCT00553319

*Reason for exclusion: Co-treatment with cognitive therapy Adult participants*

1. **Levin2018**

* Levin FR, Choi CJ, Pavlicova M, Mariani JJ, Mahony A, Brooks DJ, Nunes EV, Grabowski J. How treatment improvement in ADHD and cocaine dependence are related to one another: A secondary analysis. Drug Alcohol Depend. 2018;188:135-140.

*Reason for exclusion: Co-treatment with cognitive therapy Adult participants*

1. **Marchant2011 (NCT00506285; SLI381-404)**

* Marchant BK, Reimherr FW, Robison RJ, Olsen JL, Kondo DG. Methylphenidate transdermal system in ADHD adhd and impact on emotional and oppositional symptoms. *J Atten Disord.* 2011;15(4):295-304.
* Olsen JL, Reimherr FW, Marchant BK, Wender PH, Robison RJ. The effect of personality disorder symptoms on response to treatment with methylphenidate transdermal system in adults with attention-deficit/hyperactivity disorder. *Prim Care Companion CNS Disord.* 2012;14(5).
* Reimherr FW, Marchant BK, Olsen JL, Wender PH, Robison RJ. Oppositional defiant disorder in adults with ADHD. *J Atten Disord.* 2013;17(2):102-113.
* Gift TE, Reimherr FW, Marchant BK, Steans TA, Wender PH. Personality Disorder in Adult Attention-Deficit/Hyperactivity Disorder: Attrition and Change During Long-term Treatment. *J Nerv Ment Dis.* 2016;204(5):355-63.
* https://clinicaltrials.gov/ct2/show/NCT00506285

*Reason for exclusion: No oral formulations Adult participants*

1. **McGough2006b (NCT00466791)**

* McGough JJ, Wigal SB, Abikoff H, Turnbow JM, Posner K, Moon E. A randomized, double-blind, placebocontrolled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. *J Atten* *Disord*.2006;9(3):476-485.
* Wigal S, Turnbow J, Abikoff H, McGough J, Cohen J. Parent rated effects of transdermal methylphenidate in children with ADHD. *Int J Neuropsychopharmacol.* 2008;11(Suppl. 1):232.
* https://clinicaltrials.gov/ct2/show/NCT00466791

*Reason for exclusion: No oral formulations participants were responders*

1. **NCT00736255 (SPD489-607)**

* https://clinicaltrials.gov/ct2/show/NCT00736255

*Reason for exclusion: Combined treatment Adult participants*

1. **NCT01711021**

* https://clinicaltrials.gov/ct2/show/NCT01711021

*Reason for exclusion: No formulation of interest for the present meta-analysis (transdermal) No safety data available*

1. **NCT00218322**

* https://clinicaltrials.gov/ct2/show/NCT00218322

*Reason for exclusion: Co-treatment with CBT participants including children and adults*

1. **NCT00261872**

* https://clinicaltrials.gov/ct2/show/NCT00261872

*Reason for exclusion: Co-treatment (behavioural therapy); refers to COMBINE Study Research Group. Testing combined pharmacotherapies and behavioural interventions for alcohol dependence (the COMBINE study): a pilot feasibility study. Alcohol Clin Exp Res. 2003 Jul; 27(7):1123-31. Adult participants*

1. **NCT00514202**

* https://clinicaltrials.gov/ct2/show/NCT00514202

*Reason for exclusion: Concomitant CBT Adult participants*

1. **Pelham2001a (NCT00269789)**

* Pelham WE, Hoffman MT, Lock T. Evaluation of once-a-day OROS methylphenidate HCI (MPH)extended-release tablets versus MPH tid in children with ADHD in natural school settings. *Pediatr Res*. 2000(4):31a.
* Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107(6):E105.
* Williams L. Methylphenidate HCI extended-release tablets for children with ADHD: parent treatment prefence and satisfaction. Pediatr Res. 2001:429a.
* Swanson J. Impact of an OROS formulation of mwethylkphenidate on activity levels odf children with ADHD. Pediatr Res. 2001:429a.
* Commentary in: Connor. Once a day Concerta methylphenidate was equivalent to 3 times daily methylphenidate in children with ADHD. Evid Based Ment Health. 2002, 5, 20.
* Pooled in: Palumbo D, Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. J Child Adolesc *Psychopharmacol*. 2004;14(2):185-194.

*Reason for exclusion: Co-treatment with behavioral intervention. Participants stabilized with MPH*

1. **Pelham2005**

* Pelham WE, Burrows-Maclean L, Gnagy EM, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. Exp Clin Psychopharmacol. 2005;13(2):111-126.
* Pelham WE, Jr., Manos MJ, Ezzell CE, et al. A dose-ranging study of a methylphenidate transdermal system in children with ADHD. J Am Acad Child Adolesc Psychiatry. 2005;44(6):522-529.

*Reason for exclusion: Transdermal formulation, no oral formulations Each treatment was administered for 1 day*

1. **Pelham2011**

* Pelham WE, Jr., Waschbusch DA, Hoza B, et al. Music and video as distractors for boys with ADHD in the classroom: comparison with controls, individual differences, and medication effects. *J Abnorm Child Psychol.* 2011;39(8):1085-1098.

*Reason for exclusion: Co-treatment (behavioral intervention) No usable safety data*

1. **Pelham2016**

* Pelham WE, Fabiano GA, Waxmonsky JG, et al. Treatment Sequencing for Childhood ADHD: A Multiple- Randomization Study of Adaptive Medication and Behavioral Interventions. *J Clin Child Adolesc* *Psychol.* 2016;45(4):396-415.

*Reason for exclusion: No design of interest for the present meta-analysis medication vs behavioral parent training*

1. **Perez-Alvarez2009**

* Perez-Alvarez F, Serra-Amaya C, Timoneda-Gallart CA. Cognitive versus behavioral ADHD phenotype: what is it all about? *Neuropediatrics.* 2009;40(1):32-38.

*Reason for exclusion: No arms of interest for the present meta-analysis (medication vs. psychological treatment vs combined) No safety data*

1. **Schachar1997**

* Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, situational, and temporal effects of treatment of ADHD with methylphenidate. J Am Acad Child Adolesc Psychiatry. 1997;36(6):754-763.
* Diamond IR, Tannock R, Schachar RJ. Response to methylphenidate in children with ADHD and comorbid anxiety. J Am Acad Child Adolesc Psychiatry. 1999;38(4):402-409.
* Law SF, Schachar RJ. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? J Am Acad Child Adolesc Psychiatry. 1999;38(8):944-951.
* Summarized in: Killeen MR. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? J Child Fam Nurs. 2000;3(1):46-48.
* Follow up in: Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years: adherence, effectiveness, and adverse effects. J Am Acad Child Adolesc Psychiatry. 2004;43(5):559-567.
* Charach A, Figueroa M, Chen S, Ickowicz A, Schachar R. Stimulant treatment over 5 years: effects on growth. J Am Acad Child Adolesc Psychiatry. 2006;45(4):415-421.

*Reason for exclusion: Co-intervention: parent training No number of headache cases (n) provided*

1. **Schubiner2002**

* Downey KK, Sclrubiner H, Schuster CR. Double-blind placebo controlled stimulant trial for cocaine dependent adhd adults. NIDA Res Monogr. 2000:116.
* Schubiner H, Saules KK, Arfken CL, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol. 2002;10(3):286-294.

*Reason for exclusion: Co-intervention (CBT) Adult participants*

1. **Thurstone2010 (NCT00399763)**

* Thurstone C, Riggs PD, Salomonsen-Sautel S, Mikulich-Gilbertson SK. Randomized, controlled trial of atomoxetine for attention-deficit/hyperactivity disorder in adolescents with substance use disorder. *J Am Acad Child* *Adolesc Psychiatry.* 2010;49(6):573-582.
* Thurstone C, Salomensen-Sautel S, Riggs PD. How adolescents with substance use disorder spend research payments. *Drug Alcohol Depend.* 2010;111(3):262-264.
* https://clinicaltrials.gov/ct2/show/NCT00399763

*Reason for exclusion: Co-treatment (CBT) No number of headache cases (n) provided*

1. **Tucker2009**

* Tucker JD, Suter W, Petibone DM, et al. Cytogenetic assessment of methylphenidate treatment in pediatric patients treated for attention deficit hyperactivity disorder. *Mutat Res.* 2009;677(1-2):53-58.
* Zhou Y, Muni R, Tucker JD, Kumar V. Extendedrelease methylphenidate exposure and the frequency of cytogenetic abnormalities in children with attention-deficithyperactivity disorder. *J Child Adolesc* *Psychopharmacol. Proceedings of the 49th Annual National Institute of Mental Health (NIMH) New Clinical Drug* *Evaluation Unit (NCDEU) Meeting; 2009 June 29- July 2;Hollywood, Florida 2009;19(6):785.*

*Reason for exclusion: Co-intervention (behavioural therapy) No safety data of headache*

1. **Weiss2006a**

* Weiss M, Hechtman L. A randomized double-blind trial of paroxetine and/or Dextroamphetamine and problemfocused therapy for attention- deficit/hyperactivity disorder in adults. *J Clin Psychiatry* 2006, 67(4):611-619
* Weiss MD, Wasdell M, Gadow KD, Greenfield B, Hechtman L, Gibbins C. Clinical correlates of oppositional defiant disorder and attention-deficit/hyperactivity disorder in adults. *Postgrad Med.* 2011;123(2):177-184.
* Secondary analysis in: Weiss M, Murray C, Wasdell M, Greenfield B, Giles L, Hechtman L. A randomized controlled trial of CBT therapy for adults with ADHD with and without medication. *BMC Psychiatry.* 2012;12:30.

*Reason for exclusion: Co-treatment: psychotherapy. Adult participants*

1. **Wender1990**

* Wender PH, Reimherr FW. Bupropion treatment of attention-deficit hyperactivity disorder in adults. *Am J Psychiatry.* 1990;147(8):1018-1020.

*Reason for exclusion: Open label Adult participants*

1. **Whalen1989**

* Whalen CK, Henker B, Buhrmester D, Hinshaw SP, Huber A, Laski K. Does stimulant medication improve the peer status of hyperactive children? *J Consult Clin Psychol.* 1989;57(4):545-549.

*Reason for exclusion: Co-intervention (group CBT) No safety data*

1. **Wilens2008a (NCT00151970)**

* Frazier TW, Weiss M, Hodgkins P, Manos MJ, Landgraf JM, Gibbins C. Time course and predictors of healthrelated quality of life improvement and medication satisfaction in children diagnosed with attentiondeficit/

hyperactivity disorder treated with the methylphenidate transdermal system. *J Child Adolesc*

*Psychopharmacol.* 2010;20(5):355-364.

* López FA, Wilens TE, Wigal SB, Turnbow JM. Effects of variable wear times on transdermalmethylphenidate in attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol.* Papers of the 21st ECNP Congress; 2008 August 30 - September 3; Barcelona, Spain. 2008; Vol. 18:S561–2.
* López FA, Landgraf JM, Wilens TE. Quality of life and parent satisfaction with the methylphenidate transdermal system. European Neuropsychopharmacology. *Papers of the 21st ECNP Congress; 2008 August 30 - September 3;* *Barcelona, Spain. 2008; 4: S562*
* Manos M, Frazier TW, Landgraf JM, Weiss M, Hodgkins P. HRQL and medication satisfaction in children with ADHD treated with the methylphenidate transdermal system. *Curr Med Res Opin.* 2009;25(12):3001-3010.
* Wilens TE, Boellner SW, Lopez FA, et al. Varying the wear time of the methylphenidate transdermal system in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2008;47(6):700-708.
* https://clinicaltrials.gov/ct2/show/NCT00151970

*Reason for exclusion: Transdermal formulation No number of headache cases (n) of both treatment and placebo arm provided*

1. **Wilens2010 (NCT00586157)**

* Wilens T, Hammerness P, Utzinger L, Georgiopoulos A, Doyle R, Brodziak K, et al. Before-school ADHD symptoms and functioning in youth treated with the Methylphenidate Transdermal Patch (MTS). J Child Adolesc Psychopharmacol. Abstracts of the 49th Annual National Institute of Mental Health (NIMH)New Clinical Drug Evaluation Unit (NCDEU) Meeting;2009; June 29 - July 2; Hollywood, Florida. 2009; Vol. 19, 6:785–6.
* Wilens TE, Hammerness P, Martelon M, Brodziak K, Utzinger L, Wong P. A controlled trial of the methylphenidate transdermal system on before-school functioning in children with attention-deficit/hyperactivity disorder. *J Clin* *Psychiatry.* 2010;71(5):548-556.
* https://clinicaltrials.gov/ct2/show/NCT00586157

*Reason for exclusion: Transdermal formulation Cross-over without wash out.*

1. **Zhang2020**

* Zhang F, Zhu P, Wu L-H. Association of microRNA expression before and after drug therapy with clinical symptoms in children with attention deficit hyperactivity disorder. Chinese Journal of Contemporary Pediatrics. 2020;22(2):152-157.

*Reason for exclusion: Authors contacted to check eligibility but no response. No placebo arm; this article was written in Chinese*

**eTable 2.** Summary of characteristics of included clinical trials (*n* = 58)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Article, study ID | Country | Study design, treatment period | Participants safety analysis (male%)a | Age (y) | Comorbidity | Other remarks | Medication,  dosage | Diagnostic assessment | | Odds ratio  (95% CI) | | RoB2 | | | | | | |
| ADHD | Headache | D1 | D2 | | D3 | D4 | D5 | Overall |
| Allen (2005),  B4Z-MC-LYAS | USA | Double blind, parallel, 18w, | Treatment: n = 76 (96.1)  Placebo: n = 72 (84.7) | 7-17 | Tics, ODD, MDD, GAD, OCD | All comorbid with tics | Atomoxetine,  0.5-1.5 mg/kg,  mean 1.33 mg/kg | DSM-IV | NR | 1.10  (0.49-2.47) | | L | L | | L | L | L | L |
| Bangs (2007),  B4Z-MC-LYAX, | USA | Double blind, parallel, 9w | Treatment: n = 72 (72.2)  Placebo: n = 70 (74.3) | 12-18 | MDD | All comorbid with MDD | Atomoxetine,  1.2-1.8 mg/kg,  mean 1.51mg/kg | DSM-IV | NR | 1.80  (0.66-4.88) | | L | L | | L | L | L | L |
| Bangs (2008),  B4Z-MC-LYAX,  NCT00191698 | Europe, Australia | Double blind, parallel, 8w | Treatment: n = 156 (91.7)  Placebo: n = 70 (97.1) | 6-12 | ODD | All comorbid with ODD | Atomoxetine,  1.2 mg/kg | DSM-IV | Open-ended question | 1.53  (0.82-2.87) | | L | L | | L | L | L | L |
| Biederman (2002),  SLI 381-301 | USA | Double blind, parallel, 3w | Treatment: n = 374 (79.4)  Placebo: n = 210 (72.9) | 6-12 | not specified |  | Amphetamine,  10, 20, 30 mg (3 arms) | DSM-IV | NR | 0.80  (0.52-1.22) | | L | L | | L | L | L | L |
| Biederman (2005), Study 311 Cephalon | USA | Double blind, parallel, 9w | Treatment: n = 164 (68.9)  Placebo: n = 82 (74.4) | 6-17 | none |  | Modafinil, 170-425 mg, mean 368.5 mg | DSM-IV | Spontaneously reported | 1.41  (0.69-2.92) | | L | | L | L | L | L | L |
| Biederman (2006) | USA | Double blind, parallel, 4w | Treatment: n = 197 (74.6)  Placebo: n = 51 (74.5) | 6-13 | none |  | Modafinil,  3 arms with 300 mg, 1 arm with 400 mg | DSM-IV | Spontaneously reported | 0.55  (0.25-1.21) | | S | | L | L | L | L | S |
| Biederman (2007), NRP104-301, NCT00248092 | USA | Double blind, parallel, 4w | Treatment: n = 218 (69.3)  Placebo: n = 72 (69.4) | 6-12 | none |  | Amphetamine,  30, 50, 70 mg (3 arms) | DSM-IV-TR | Open-ended question | 1.26  (0.52-3.03) | | L | | L | L | L | L | L |
| Biederman (2008),  SPD503-301, NCT00152009 | USA | Double blind, parallel, 8w | Treatment: n = 259 (74.5)  Placebo: n = 86 (74.4) | 6-17 | none |  | Guanfacine,  2, 3, 4 mg (3 arms) | DSM-IV-TR | NR | 1.10  (0.63-1.94) | | L | | L | L | L | L | L |
| Block (2009),  B4Z-US-LYCC, NCT00486122, | USA | Double blind, parallel, 6w | Treatment: n = 195 (71.8)  Placebo: n = 92 (74.2) | 6-12 | ODD |  | Atomoxetine,  0.47-1.81 mg/kg,  mean 1.25 and 1.26 mg/kg (AM and PM) | DSM-IV-TR | Open-ended question | 2.13  (0.69-6.50) | | L | | L | L | L | L | L |
| Brams (2018), NCT02466425 | USA | Double blind, parallel, 4w | Treatment: n = 132 (65.2)  Placebo: n = 131 (58.8) | 6-17 |  |  | Amphetamine,  12.5 or 25 mg | DSM-IV-TR | NR | 1.15  (0.54-2.47) | | S | | L | L | L | L | S |
| Childress (2009), CRIT124E2305, NCT00301236 | USA | Double blind, parallel, 5w | Treatment: n = 182 (63.8)  Placebo: n = 63 (66.2) | 6-12 | none |  | Methylphenidate,  10, 20, 30 mg (3 arms) | DSM-IV-TR | NR | 0.95  (0.40-2.25) | | L | | L | L | L | L | L |
| Coghill (2013), SPD489-325 | Europe  (10 countries) | Double blind, parallel, 7w | Treatment (A): n = 111 (78.4)  Treatment (M): n = 111 (81.1)  Placebo: n = 110 (82.7) | 6-17 | ODD, and other unspecified |  | Amphetamine,  30-70 mg,  mean 53.8 mg;  Methylphenidate,  18-54 mg,  mean 45.4 mg | DSM-IV-TR | NR | A: 0.67  (0.33-1.37)  M: 0.99  (0.51-1.91) | | L | | L | L | L | L | L |
| Connor (2010), SPD503-307, NCT00367835 | USA | Double blind, parallel, 9w | Treatment: n = 136 (64.0)  Placebo: n = 78 (76.9) | 6-12 |  |  | Guanfacine,  1-4 mg,  mean 2.9 mg | DSM-IV-TR | NR | 1.29  (0.64-2.62) | | L | | L | L | L | L | L |
| CRIT124DUS02 (2004) | USA | Double blind, crossover, 4w | Treatment: n = 102 (0)  Placebo: n = 101 (0) | 12-17 |  | All females | Methylphenidate,  20-60 mg | DSM-IV-TR | NR | 1.52  (0.76-3.04) | | S | | L | L | L | L | S |
| Daviss (2008), NCT00031395 | USA | Double blind, parallel, 16w | Treatment (C): n = 31 (87.1)  Treatment (M): n = 29 (82.8)  Placebo: n = 30 (76.7) | 7-12 | ODD, CD |  | Clonidine,  mean 0.24 mg;  Methylphenidate,  mean 30.2 mg | DSM-IV | Spontaneously reported | C: 1.73  (0.38-7.99)  M: 0.32  (0.03-3.28) | | L | | L | L | L | L | L |
| Dell’Agnello (2009) | Italy | Double blind, parallel, 8w | Treatment: n = 107 (93.3)  Placebo: n = 32 (90.6) | 6-15 | ODD, GAD, OCD, SAD, MDD, panic disorder, specific phobia, adjustment disorder, dysthymia | All comorbid with ODD | Atomoxetine,  0.85-1.33 mg/kg,  mean 1.10 mg/kg | DSM-IV | NR | 1.92  (0.61-6.02) | | S | | S | L | L | L | S |
| Dittmann (2011) | Germany | Double blind, parallel, 9w | Treatment: n = 121 (86.0)  Placebo: n = 59 (81.4) | 6-17 | ODD, CD, adjustment disorder | All comorbid with ODD or CD | Atomoxetine,  1.2 mg/kg | DSM-IV-TR | Open-ended question | 1.37  (0.59-3.18) | | L | | L | L | L | L | L |
| Findling (2010), NCT00499863, SPD485-40 | USA | Double blind, parallel, 7w | Treatment: n = 145 (75.2)  Placebo: n = 72 (73.6) | 13-17 |  | Transdermal | Methylphenidate,  10-30 mg,  mean 24.3 mg | DSM-IV-TR | Spontaneously reported | 0.99  (0.42-2.33) | | L | | S | L | S | L | S |
| Findling (2011),  SPD 489-305, NCT00735371 | USA | Double blind, parallel, 4w | Treatment: n = 233 (70.6)  Placebo: n = 77 (68.4) | 13-17 |  |  | Amphetamine,  30, 50, 70 mg (3 arms) | DSM-IV-TR | Spontaneously reported | 1.14  (0.54-2.44) | | L | | L | L | L | L | L |
| Froehlich (2018), NCT01727414 | USA | Double blind, crossover, 1w  (the first week data included) | Treatment: n = 108 (71.3)  Placebo: n = 53 (71.3) | 7-11 | ODD, CD, OCD, PTSD, MDD, SAD, GAD, dysthymia, social phobia, panic disorder | All stimulant-naïve | Methylphenidate,  18 mg | DSM-IV | Parent report questionnaire | 2.26  (0.96-5.35) | | S | | L | L | L | L | S |
| Gau (2007),  B4Z-TW-S010, NCT00485459 | Taiwan | Double blind, parallel, 6w | Treatment: n = 72 (90.3)  Placebo: n = 34 (85.3) | 6-16 | ODD, CD |  | Atomoxetine,  1.2-1.8 mg/kg, mean 1.4 mg/kg | DSM-IV | Open-ended question | 1.72  (0.34-8.77) | | L | | L | L | L | L | L |
| Geller (2007),  B4Z-US-LYBP | USA | Double blind, parallel, 10w | Treatment: n = 77 (62.1)  Placebo: n = 80 (67.4) | 8-17 |  | All comorbid with anxiety disordersb | Atomoxetine,  1.2-1.8 mg/kg,  mean 1.43 mg/kg | DSM-IV | Open-ended question | 1.74  (0.64-4.75) | | L | | L | L | L | L | L |
| Greenhill (2002) | USA | Double blind, parallel, 3w | Treatment: n = 155 (82.6)  Placebo: n = 161 (81.1) | 6-16 |  |  | Methylphenidate,  20-60 mg,  mean 36.8 mg | DSM-IV | Participants: spontaneously reported (data used);  Parents and teachers:  questionnaire | Participants:  1.48  (0.76-2.88);  Parents:  1.23  (0.71-2.15) | | S | | L | L | L | L | S |
| Greenhill (2006a), Study 309 Cephalon | USA | Double blind, parallel, 9w | Treatment: n = 131 (72.5)  Placebo: n = 67 (73.1) | 6-17 |  |  | Modafinil,  170-425 mg,  mean 361.4 mg | DSM-IV | Spontaneously reported | 2.89  (1.14-7.36) | | L | | L | L | L | L | L |
| Greenhill (2006b), CRIT124E2301 | USA | Double blind, parallel, 7w | Treatment: n = 53 (58.5)  Placebo: n = 47 (70.0) | 6-17 |  | Classroom setting | Methylphenidate,  5-30 mg,  mean 24 mg | DSM-IV | Spontaneously reported | 2.73  (0.89-8.36) | | S | | L | L | L | L | S |
| Griffiths (2018), ACTRN 12607000535471 | Australia | Double blind, crossover, 6w | Treatment: n = 107 (78.4)  Placebo: n = 113 (78.4) | 6-17 | SAD, GAD, MDD, OCD, ODD, CD, PTSD, social anxiety, |  | Atomoxetine,  1.0-1.4 mg/kg,  mean 1.35 mg/kg | DSM-IV | Parent report questionnaire | 2.16  (0.39-12-02) | | L | | L | L | L | L | L |
| Harfterkamp (2012), NCT00380692 | the Netherlands | Double blind, parallel, 8w | Treatment: n = 48 (87.5)  Placebo: n = 49 (83.7) | 6-17 | ASD | All comorbid with ASD | Atomoxetine,  1.2 mg/kg | DSM-IV-TR | Open-ended question | 1.48  (0.56-3.93) | | L | | L | L | L | L | L |
| Hervas (2014), SPD503-316, NCT01244490, EudraCT: 2010- 018579-12 | Europe, USA, Canada | Double blind, parallel, 13w | Treatment (G): n = 114 (66.7)  Treatment (A): n = 112 (77.7)  Placebo: n = 111 (77.5) | 6-17 | ODD |  | Guanfacine,  1-7 mg,  mean 0.09 mg/kg;  Atomoxetine,  0.5-1.4 mg/kg,  mean 1.03 mg/kg | DSM-IV | NR | G: 1.11  (0.61-2.03)  A: 0.76  (0.40-1.44) | | L | | L | L | L | L | L |
| Ichikawa (2020), Japic CTI-152770 | Japan | Double blind, parallel, 4w | Treatment: n = 57 (82.5)  Placebo: n = 19 (84.2) | 6-17 |  |  | Amphetamine,  30, 50, 70 mg (3 arms) | DSM-5 | NR | no case in placebo arm | | S | | L | L | L | L | S |
| Kahbazi (2009) | Iran | Double blind, parallel, 6w | Treatment: n = 23 (78.3)  Placebo: n = 23 (73.9) | 6-15 |  |  | Modafinil,  200-300 mg | DSM-IV-TR | Checklist administered by a child  psychiatrist | 2.10  (0.18-24.87) | | L | | L | L | L | L | L |
| Kelsey (2004),  B4Z-US-LYBG | USA | Double blind, parallel, 8w | Treatment: n = 131 (70.7)  Placebo: n = 63 (70.3) | 6-12 | ODD, CD |  | Atomoxetine,  1.8 mg/kg | DSM-IV | Open-ended question | 0.44  (0.17-1.18) | | L | | L | L | L | L | L |
| Kollins (2011), SPD503-206, NCT00150592 | USA | Double blind, parallel, 6w | Treatment: n = 121 (66.1)  Placebo: n = 57 (77.2) | 6-17 |  | Laboratory classroom | Guanfacine,  1-3 mg,  mean 0.052 mg/kg | DSM-IV-TR | NR | 1.38  (0.63-3.00) | | L | | L | L | L | L | L |
| Martenyi (2010), B4Z-MW-LYCZ, NCT00386581 | Russia | Double blind, parallel, 6w | Treatment: n = 72 (87.5)  Placebo: n = 33 (81.8) | 6-16 |  |  | Atomoxetine,  1.2-1.8 mg/kg | DSM-IV | Open-ended question | 1.16  (0.21-6.30) | | L | | L | L | L | L | L |
| Mattingly (2020),  NCT03325881 | USA | Double blind, parallel, 4w | Treatment: n = 45 (67.4)  Placebo: n = 43 (60.0) | 6-12 |  |  | Methylphenidate,  6.25mg | DSM-5 | NR | 0.70  (0.15-3.31) | | L | | L | L | L | L | L |
| Michelson (2001), B4Z-MC-LYAC | USA | Double blind, parallel, 8w | Treatment: n = 211 (71.4)  Placebo: n = 83 (71.4) | 8-18 | ODD, GAD |  | Atomoxetine, 0.5, 1.2, 1.8 mg/kg (3 arms) | DSM-IV | Open-ended question | 1.07  (0.59-1.96) | | L | | L | L | L | L | L |
| Michelson (2002), B4Z-MC-LYAT | USA | Double blind, parallel, 6w | Treatment: n = 85 (70.6)  Placebo: n = 85 (70.6) | 6-16 | ODD, GAD, depression, specific phobia |  | Atomoxetine,  1.0-1.5 mg/kg | DSM-IV | Open-ended question | 1.17  (0.54-2.52) | | L | | L | L | L | L | L |
| Montoya (2009),  B4Z-XM-LYDM, NCT00191945 | Spain | Double blind, parallel, 12w | Treatment: n = 100 (79.0)  Placebo: n = 51 (80.4) | 6-15 | ODD, tics, anxiety disorder, affective disorder | All treatment-naïve | Atomoxetine,  0.8-1.4mg/kg,  mean 1.2 mg/kg | DSM-IV-TR | NR | 3.51  (0.98-12.55) | | L | | L | L | L | L | L |
| NCT00936299 (2019) | USA | Quadruple blind, parallel, 16w | Treatment: n = 53 (86.8)  Placebo: n = 52 (88.5) | 13-19 | SUD | All with SUD; add-on CBT | Bupropion,  300 mg | DSM-IV | NR | 0.79  (0.33-1.93) | | S | | S | L | L | L | S |
| Newcorn (2008), B4Z-MC-LYBI | USA | Double blind, parallel, 6w | Treatment (A): n = 221 (77.5)  Treatment (M): n = 219 (70.9)  Placebo: n = 74 (74.3) | 6-16 | ODD |  | Atomoxetine,  0.8-1.8 mg/kg,  mean 1.45 mg/kg;  Methylphenidate,  18-54 mg,  mean 39.9 mg | DSM-IV | Open-ended question | A: 2.05  (0.87-4.81)  M: 1.23  (0.51-2.98) | | L | | L | L | L | L | L |
| Newcorn (2013), SPD503-314, NCT00997984 | USA | Double blind, parallel, 8w | Treatment: n = 221 (67.9)  Placebo: n = 112 (75.9) | 6-12 |  |  | Guanfacine,  1-4 mg,  mean 0.084 mg/kg | DSM-IV-TR | Spontaneously reported | 1.68  (0.84-3.36) | | S | | H | L | H | L | H |
| Newcorn (2017)c, SPD489-405, NCT01552915 | USA | Double blind, parallel, 8w | Treatment (A): n = 184 (66.3)  Treatment (M): n = 184 (66.3)  Placebo: n = 91 (67.0) | 13-17 |  |  | Amphetamine,  30-70 mg,  mean 55.15 mg;  Methylphenidate,  18-72 mg,  mean 44.47 mg | DSM-IV-TR | NR | A: 2.15  (0.90-5.14)  M: 2.15  (0.90-5.14) | | L | | L | L | L | L | L |
| Newcorn (2017)c, SPD489-406, NCT01552902 | USA, Canada, Germany, Hungary, Sweden | Double blind, parallel, 6w | Treatment (A): n = 218 (68.5)  Treatment (M): n = 219 (61.9)  Placebo: n = 110 (69.1) | 13-17 |  |  | Amphetamine,  70 mg;  Methylphenidate,  72 mg | DSM-IV-TR | NR | A: 2.00  (0.92-4.35)  M: 2.13  (0.99-4.62) | | L | | L | L | L | L | L |
| Pliszka (2000) | USA | Double blind, parallel, 3w | Treatment (A): n = 20 (NR)  Treatment (M): n = 20 (NR)  Placebo: n = 18 (NR) | 6-12 | ODD, CD, anxiety disorder |  | Amphetamine,  10-30 mg,  mean 12.5 mg;  Methylphenidate,  10-50 mg,  mean 25.2 mg | DSM-IV | Parent report questionnaire | A: 1.89  (0.16-22.79)  M: no case | | L | | L | L | L | L | L |
| Pliszka (2017), NCT02520388 | USA | Double blind, parallel, 3w | Treatment: n = 81 (67.9)  Placebo: n = 80 (72.5) | 6-12 |  |  | Methylphenidate,  40-80 mg | DSM-5 | Spontaneously reported | 2.08  (0.60-7.21) | | S | | S | L | S | L | S |
| Riggs (2011), NCT00264797, | USA | Double blind, parallel, 16w | Treatment: n = 151 (80.8)  Placebo: n = 152 (77.0) | 13-18 | SUD, CD, MDD | All with SUD; add-on CBT | Methylphenidate,  72 mg | DSM-IV | NR | 1.19  (0.75-1.87) | | S | | L | L | L | L | S |
| Rugino (2003) | USA | Double blind, parallel, 6w | Treatment: n = 11 (63.6)  Placebo: n = 11 (63.6) | 5-15 | ODD, CD, SAD, specific phobia, enuresis |  | Modafinil,  200-300 mg,  mean 264 mg | DSM-IV | NR | no case in placebo arm | | L | | L | L | L | L | L |
| Rugino (2018), NCT01156051 | USA | Double blind, parallel, 5w | Treatment: n = 11 (81.8)  Placebo: n = 16 (50.0) | 6-12 |  |  | Guanfacine,  1-4 mg,  mean 3 mg | DSM-IV-TR | NR | 4  (0.58-27.41) | | S | | S | L | L | L | S |
| Sallee (2009), SPD503-304, NCT00150618 | USA | Double blind, parallel, 9w | Treatment: n = 256 (73.2)  Placebo: n = 66 (68.2) | 6-17 |  |  | Guanfacine,  1, 2, 3, 4 mg (4 arms) | DSM-IV-TR | NR | 2.2  (0.95-5.10) | | L | | L | L | L | L | L |
| Spencer (2002)d, B4Z-MC-HFBD, B4Z-MC-HFBK | USA | Double blind, parallel, 12w | Treatment: n = 129 (76.0)  Placebo: n = 124 (83.1) | 7-12 |  |  | Atomoxetine,  maximum 2 mg/kg | DSM-IV | Spontaneously reported | 1.10  (0.64-1.90) | | L | | L | L | L | L | L |
| Spencer (2006), SLI381-314, NCT00507065 | USA | Double blind, parallel, 4w | Treatment: n = 233 (65.0)  Placebo: n = 54 (67.3) | 13-17 |  |  | Amphetamine,  10, 20, 30, 40 mg (4 arms) | DSM-IV-TR | NR | 0.68  (0.33-1.41) | | L | | L | L | L | L | L |
| Svanborg (2009), B4Z-SO-LY15, EUCTR2004-003941-42-SE, NCT00191542 | Sweden | Double blind, parallel, 10w | Treatment: n = 49 (79.6)  Placebo: n = 50 (82.0) | 7-15 | Tics, ODD, depression | All stimulant-naïve | Atomoxetine,  0.6-1.4 mg/kg,  mean 1.1 mg/kg | DSM-IV | NR | 2.89  (1.15-7.26) | | L | | L | L | L | L | L |
| Swanson (2006) | USA | Double blind, parallel, 7w | Treatment: n = 125 (74.4)  Placebo: n = 64 (65.6) | 6-17 |  |  | Modafinil,  340 or 425 mg | DSM-IV-TR | Parent report questionnaire | 1.23  (0.53-2.88) | | S | | L | L | L | L | S |
| Takahashi (2009), B4Z-JE-LYBC, NCT00191295 | Japan | Double blind, parallel, 8w | Treatment: n = 183 (85.8)  Placebo: n = 62 (83.9) | 6-17 |  |  | Atomoxetine,  0.5, 1.2, 1.8 mg/kg (3 arms) | DSM-IV | NR | 0.93  (0.28-3.03) | L | | | L | L | L | L | L |
| Wehmeier (2012), B4Z-SB-LYDV, NCT00546910 | Germany | Double blind, parallel, 8w | Treatment: n = 63 (74.6)  Placebo: n = 62 (80.6) | 6-12 | ODD, CD, Tics, mood disorder |  | Atomoxetine,  1.2 mg/kg | DSM-IV-TR | Open-ended question | 0.57  (0.13-2.50) | L | | | L | L | L | L | L |
| Wigal (2004) | USA | Double blind, parallel, 4w | Treatment: n = 90 (90.0)  Placebo: n = 42 (83.3) | 6-17 |  |  | Methylphenidate,  mean 18.25 mg (d-MPH), 32.14 mg (d,l-MPH) | DSM-IV | NR | 2.21  (0.70-7.04) | S | | | L | L | L | L | S |
| Wigal (2015), NCT01239030, | USA | Double blind, parallel, 1w | Treatment: n = 183 (67.8)  Placebo: n = 47 (63.8) | 6-18 |  |  | Methylphenidate, 10, 15, 20, 40 mg (4 arms) | DSM-IV-TR | NR | 1.17  (0.38-3.61) | S | | | S | L | S | L | S |
| Wilens (2015), SPD503-312, EUCTR2011-002221-21, NCT01081132 | USA | Double blind, parallel, 13w | Treatment: n = 157 (65.6)  Placebo: n = 155 (63.9) | 13-17 | ODD |  | Guanfacine,  1-7 mg,  mean 4.3 mg | DSM-IV-TR | NR | 1.66  (0.96-2.84) | L | | | L | L | L | L | L |

NR, not reported; RoB 2, Revised Cochrane risk-of-bias tool for randomized trials; ASD, autism spectrum disorder; MDD, major depressive disorder; ODD, oppositional defiant disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; CD, conduct disorder; SUD, substance use disorders; SAD, separation anxiety disorder; PTSD, post-traumatic stress disorder; CBT, cognitive-behavioral therapy;

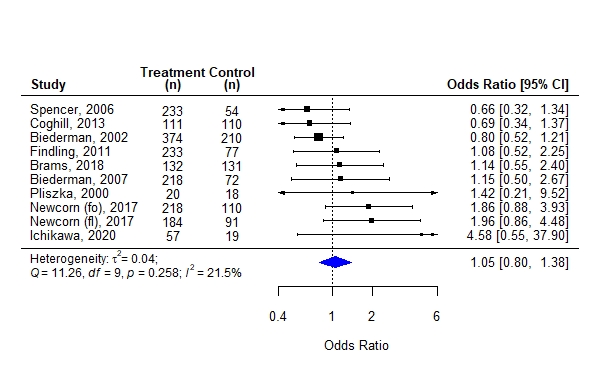
aSex distribution in the intention-to-treat sample

bAnxiety disorders: generalized anxiety disorder, separation anxiety disorder, and/or social phobia

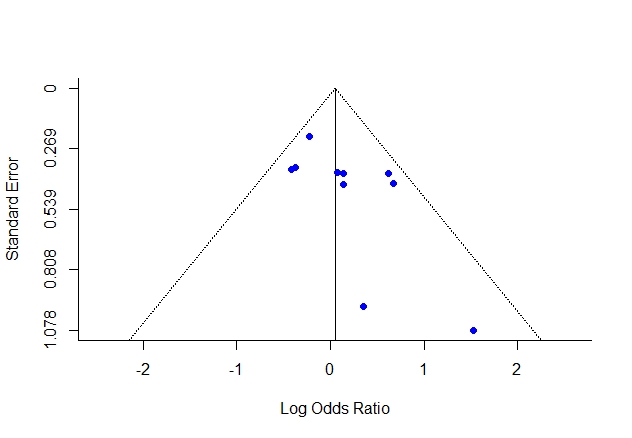
cThis article reported the results of two studies

dThis article reported the pooled data of two studies

**eFigure 3.** Forest plot of risk of headache between amphetamine treatment groups and placebo groups

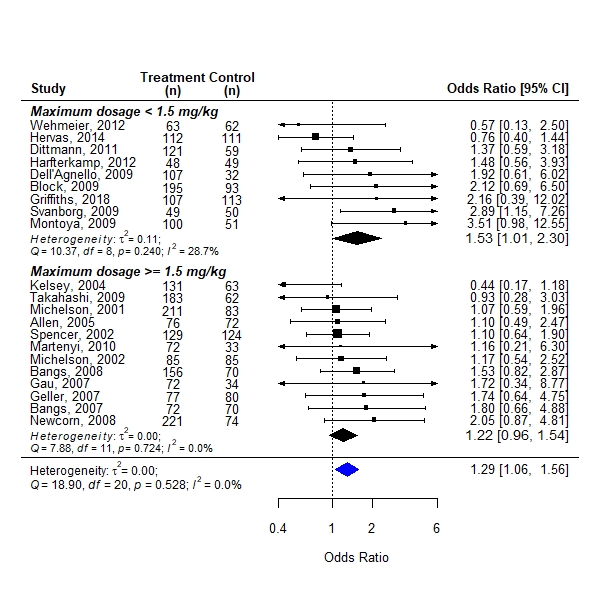


**eFigure 4.** Funnel plot of trials on the association between amphetamine and headache among children with ADHD

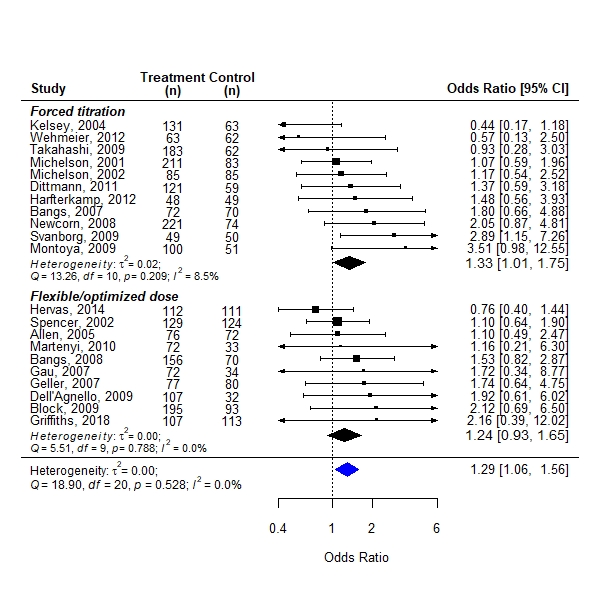


Egger's test: *t* = 2.10, *df* = 8, *p* = 0.069

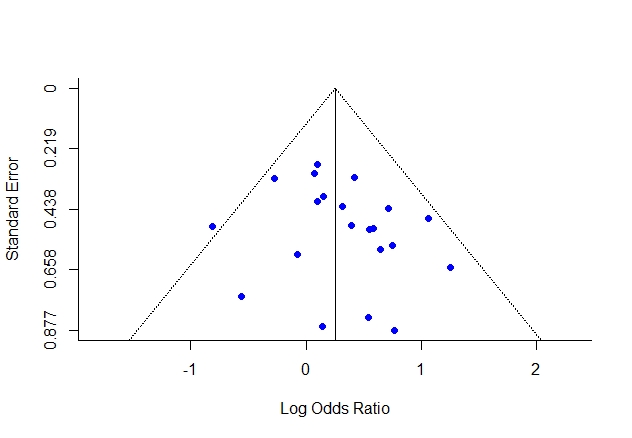
**eFigure 5.** Forest plot of risk of headache between atomoxetine treatment groups and placebo groups, with subgroup analysis based on maximum dosage



**eFigure 6.** Forest plot of risk of headache between atomoxetine treatment groups and placebo groups, with subgroup analysis based on dosing strategy

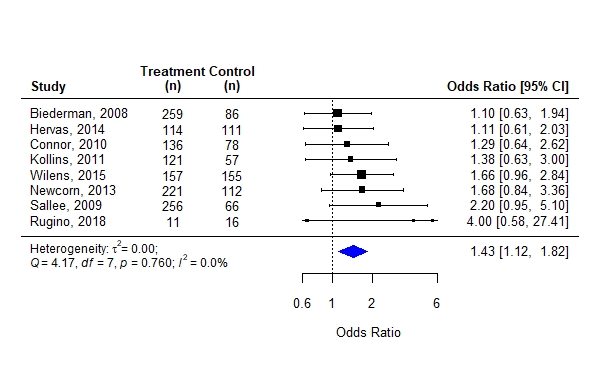


**eFigure 7.** Funnel plot of trials on the association between atomoxetine and headache among children with ADHD

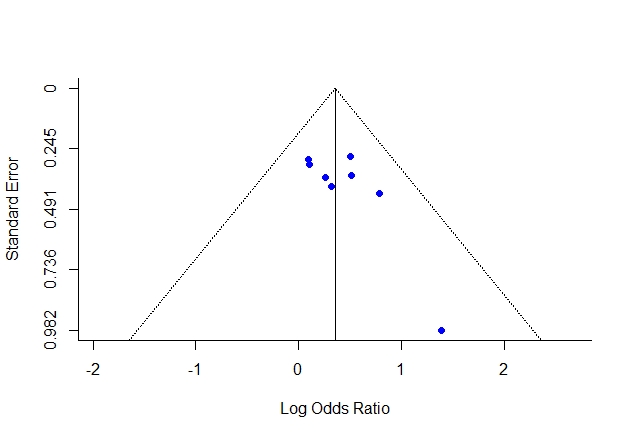


Egger's test: *t* = 1.27, *df* = 19, *p* = 0.221

**eFigure 8.** Forest plot of risk of headache between guanfacine treatment groups and placebo groups

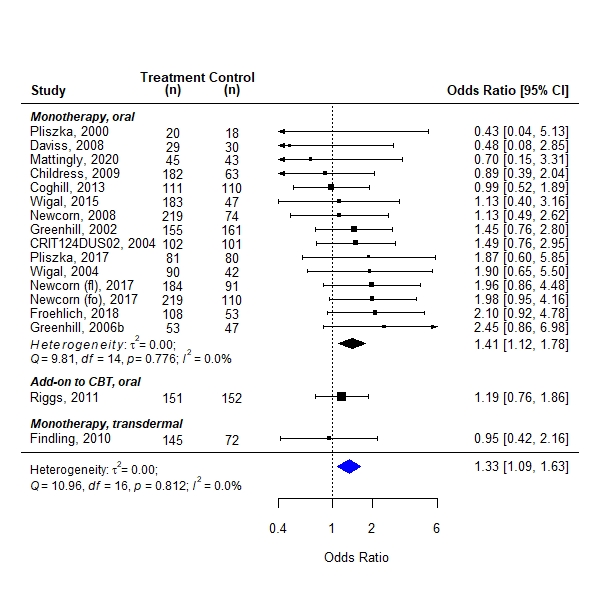


**eFigure 9.** Funnel plot of trials on the association between guanfacine and headache among children with ADHD

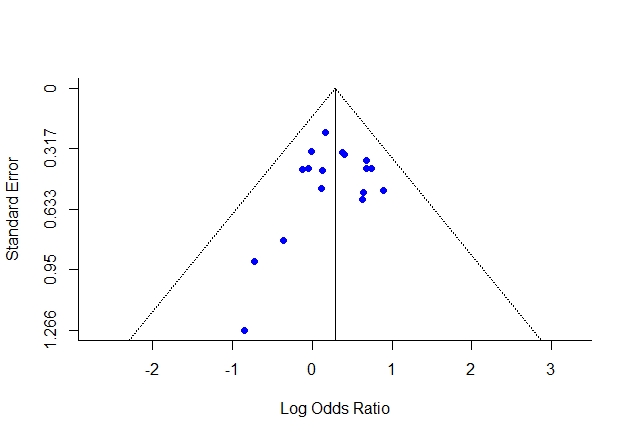


Egger's test: *t* = 2.05, *df* = 20, *p* = 0.086

**eFigure 10.** Forest plot of risk of headache between methylphenidate treatment groups and placebo groups

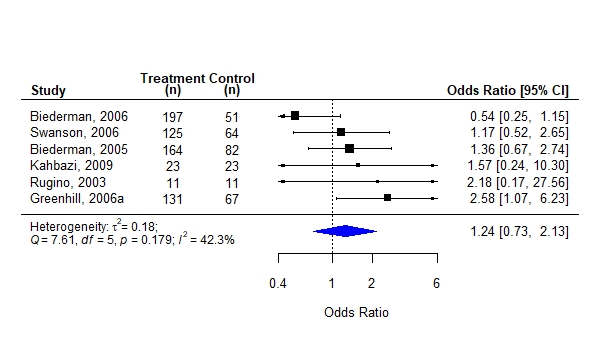


**eFigure 11**. Funnel plot of trials on the association between methylphenidate and headache among children with ADHD

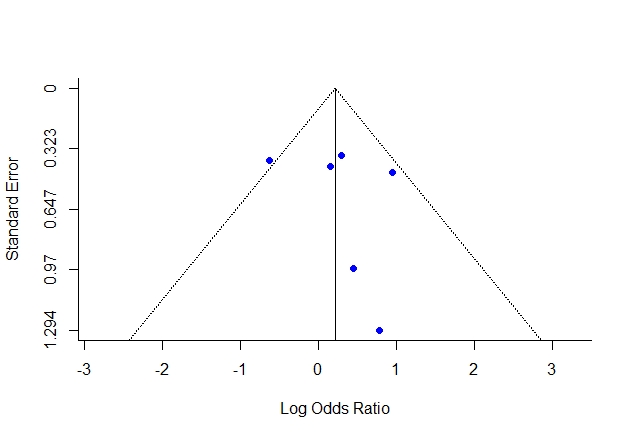


Egger's test: *t* = -0.58, *df* = 15, *p* = 0.570

**eFigure 12.** Forest plot of risk of headache between modafinil treatment groups and placebo groups



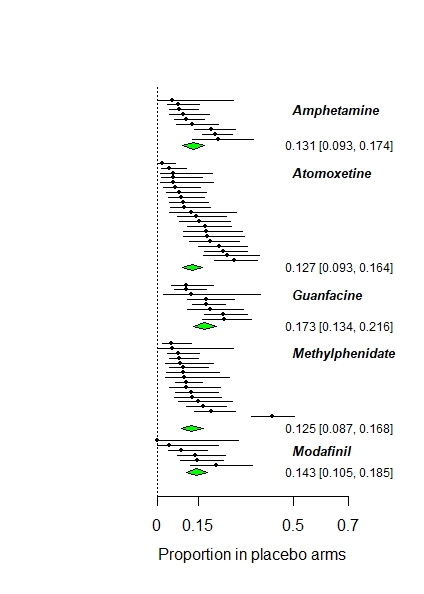
**eFigure 13.** Funnel plot of trials on the association between modafinil and headache among children with ADHD



Egger's test: *t* = 0.59, *df* = 4, *p* = 0.589

**eFigure 14.** Caterpillar plot of trials on the prevalence of headache among children with ADHD treated with ADHD medications

**eFigure 15.** Caterpillar plot of trials on the prevalence of headache among children with ADHD in placebo arms



**eFigure 16.** Caterpillar plot of trials on the prevalence of headache among youths with ADHD in placebo arms based on different age

