

Supplementary information

Efficacy and safety of medication for attention-deficit hyperactivity disorder in children and adolescents with common comorbidities: A systematic review

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Additional file 1 Electronic search strategies

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations

- 1 (adhd or hkd or addh or hyperkine* or "attention deficit" or hyper-activ* or hyperactiv* or overactiv* or inattentive or impulsiv*).ti,ab.
- 2 atomoxetine/ or methylphenidate/ or amphetamine/ or Methamphetamine/ or Dextroamphetamine/ or dexmethylphenidate/
- 3 ((extended-release adj1 guanfacine) or ("extended release" adj1 guanfacine) or GXR or intuniv or atomoxetine or ritalin or methylphenidate or strattera or lisdexamfetamine or vyvanse or focalin or concerta or adderall or dexmethylphenidate or dextroamphetamine or dexamphetamine or mixed-amphetamine or "mixed amphetamine").mp.
- 4 1 and (2 or 3)
- 5 Asperger Syndrome/ or Autistic Disorder/ or Autism Spectrum Disorder/ or (asperger* or autis*).mp.
- 6 Tic Disorders/ or (tic* or tourette*).mp.
- 7 "Attention Deficit and Disruptive Behavior Disorders"/ or (oppositional or defiant or disruptive or conduct).mp.
- 8 Depression/ or ("major depression" or "major depressive").ti,ab.
- 9 Anxiety Disorders/ or anxiety.ti,ab.
- 10 5 or 6 or 7 or 8 or 9
- 11 4 and 10
- 12 exp rodent/ or exp dogs/ or exp cats/ or exp rabbits/ or exp horses/ or exp ruminants/ or exp swine/ or exp InVitro, techniques/ or exp cells, cultured/ or exp stem cell research/ or exp animal experimentation/ or exp disease models, animals/ or exp models, animal/ or exp animal tissue/ or (rat* or mice or mouse or cat* or dog* or vitro or vivo or animal*).ti.
- 13 (animals not human).tw.
- 14 12 or 13
- 15 11 not 14
- 16 (genetic or gene or polymorphism or congenital or epilep* or nicotine or pregnan*).ti,ab.
- 17 15 not 16
- 18 limit 17 to (address or autobiography or bibliography or biography or clinical conference or clinical trial, veterinary or clinical trials, veterinary as topic or clinical trial protocol or clinical trial protocols as topic or congress or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or "expression of concern" or government document or interactive tutorial or interview or lecture or legal case or legislation or news or newspaper article or observational study, veterinary or patient education handout or personal narrative or portrait or "review" or video-audio media or webcasts)
- 19 (meta-analysis or metaanalysis or pooled or (systematic adj review)).mp.
- 20 18 and 19
- 21 (17 not 18) or 20

Embase

- 1 (adhd or hkd or addh or hyperkine* or "attention deficit" or hyper-activ* or hyperactiv* or overactiv* or inattentive or impulsiv*).ti,ab.
- 2 (GXR or intuniv or atomoxetine or ritalin or methylphenidate or strattera or lisdexamfetamine or vyvance or focalin or concerta or adderall or dexmethylphenidate or dextroamphetamine or dexamphetamine or mixed-amphetamine or "mixed amphetamine").mp.
- 3 (extended-release or "extended release").ti,ab.
- 4 guanfacine.mp.
- 5 3 and 4
- 6 exp atomoxetine/ or exp methylphenidate/ or exp amphetamine/ or exp dexmethylphenidate/ or exp dexamphetamine/ or exp methamphetamine/
- 7 1 and (2 or 5 or 6)
- 8 autis*.mp. or autism/
- 9 Asperger syndrome/ or asperger*.mp.
- 10 tic/ or Gilles de la Tourette syndrome/ or (tic* or tourette*).mp.
- 11 oppositional defiant disorder/ or (oppositional or defiant or disruptive or conduct).mp.
- 12 anxiety disorder/ or generalized anxiety disorder/ or anxiety.ti,ab.
- 13 major depression/ or adolescent depression/ or ("major depression" or "major depressive").ti,ab.
- 14 8 or 9 or 10 or 11 or 12 or 13
- 15 7 and 14
- 16 exp rodent/ or exp dogs/ or exp cats/ or exp rabbits/ or exp horses/ or exp ruminants/ or exp swine/ or exp InVitro, techniques/ or exp cells, cultured/ or exp stem cell research/ or exp animal experimentation/ or exp disease models, animals/ or exp models, animal/ or exp animal tissue/ or (rat* or mice or mouse or cat* or dog* or vitro or vivo or animal*).ti.
- 17 (animals not human).tw.
- 18 16 or 17
- 19 15 not 18
- 20 (genetic or gene or polymorphism or congenital or epilep* or nicotine or pregnan*).ti,ab.
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- 22 limit 21 to (books or chapter or conference abstract or conference paper or "conference review" or tombstone)
- 23 21 not 22
- 24 limit 23 to (books or chapter or conference abstract or conference paper or "conference review" or "review" or short survey or tombstone)
- 25 (meta-analysis or metaanalysis or pooled or (systematic adj review)).mp.
- 26 24 and 25
- 27 23 not 24
- 28 26 or 27

Additional file 1 Table S1 Cochrane risk of bias rating of placebo-controlled trials for which effect size data were reported

Item	Allen, 2005*	Bangs, 2007*	Connor, 2010*	Geller, 2007*	Griffiths, 2018	Harfterkamp, 2012	Kaplan, 2004	Newcorn, 2005	Scahill, 2001	Scahill, 2015
Sequence generation	-	-	-	-	-	-	-	?	?	?
Allocation concealment	-	-	-	-	-	-	-	?	?	-
Blinding participants/parents	-	-	-	-	-	-	-	?	-	?
Blinding therapist	-	-	-	-	-	-	-	?	-	-
Blinding assessor	-	-	-	-	-	-	-	?	-	-
Incomplete data outcome	-	-	-	-	-	-	?	?	?	-
Selective reporting	+	-	-	+	?	-	?	?	?	-

* Risk of bias assessed by Cortese et al, Lancet Psychiatry. 2018;5(9):727-38.
 Green/-, low risk of bias; Red/+, high risk of bias; Yellow/?, unknown risk of bias.

Additional file 1 Table S2 Other efficacy findings

Citation	Study design	Number of patients	Comorbidities	Main findings for CGI for ADHD
Autism spectrum disorder				
Pearson, 2013 [43]	RCT – crossover MPHs vs PBO	<i>n</i> = 24	Autistic disorder: 79.2% PDD-NOS: 8.3% Asperger: 12.5%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-I scores were found by the psychiatrist ($F[3,69]=15.49, P < 0.001$) and psychologist ($F[3,69]=12.62, P < 0.001$) with MPHs; CGI-S scores significantly improved with MPHs as assessed by the psychiatrist ($F[3,69]=7.62, P < 0.001$) and psychologist ($F[3,69]=12.46, P < 0.001$)
Patra, 2019 [18]	MA ATX vs PBO	<i>n</i> = 241	NR	<ul style="list-style-type: none"> Significantly greater improvement in CGI-I with ATX (relative risk 2.37 [95% CI: 1.38, 4.06])
Harfterkamp, 2012 [38]	RCT – parallel ATX vs PBO	<i>n</i> = 97 OLE, <i>n</i> = 88	Autistic disorder: 59.8% PDD-NOS: 33.0% Asperger: 5.2%	<ul style="list-style-type: none"> CGI-ADHD-I response rate numerically higher for ATX (20.9% vs 8.7%)
NCT00498173 [41]	RCT – parallel ATX vs PBO	<i>n</i> = 60	Autistic disorder: 38.3% PDD-NOS: 38.3% Asperger: 23.3%	NR
Handen, 2015 [36]	RCT – parallel ATX±parent training vs PBO±parent training	<i>n</i> = 128	Autistic disorder: 44.5% PDD-NOS: 39.1% Asperger: 16.4%	<ul style="list-style-type: none"> CGI-ADHD-I response rate significantly higher for ATX with or without parent training (48.4%, 46.9% vs 29.0%, 19.4%)
Scahill, 2015 [45]	RCT – parallel GXR vs PBO	<i>n</i> = 62	Autistic disorder: 82.3% PDD-NOS: 14.5% Asperger: 3.2%	<ul style="list-style-type: none"> CGI-I response rate significantly higher with GXR (50.0% vs 9.4%), $P = 0.0001$
Handen, 2008 [37]	RCT – crossover GXR vs PBO	<i>n</i> = 11	Intellectual disability or autism	<ul style="list-style-type: none"> Significantly greater improvements in CGI-I scores for GXR ($2.82±0.9$ vs $3.82±0.6, P < 0.005$), but not CGI-S ($4.36±0.5$ vs $4.82±0.6, P < 0.070$)
Oppositional defiant disorder				
Spencer, 2006 [46]	RCT – parallel AMPs vs PBO	<i>n</i> = 308	ODD: 79.2%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-ADHD-I scores with AMPs 20 mg (61.9%, $P < 0.001$), 30 mg (54.9%, $P < 0.008$), and 40 mg (60.4%, $P < 0.001$) vs PBO (26.5%)
Schwartz, 2014 [20]	MA ATX vs PBO	<i>n</i> = 3697	ODD: various%	<ul style="list-style-type: none"> Standardized mean difference for CGI-ADHD-I: -0.55 ([95% CI: $-0.66, -0.44$], $P < 0.0001$). Standardized mean difference for CGI-ADHD-S: -0.57 ([95% CI: $-0.71, -0.44$], $P < 0.0001$)
Cheng, 2007 [17]	MA ATX vs PBO	<i>n</i> = 213	ODD: NR%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-S scores with ATX (standardized mean difference: -0.598 [95% CI: $-0.849, -0.347$], $P < 0.05$)
Newcorn, 2005 [42]	RCT – parallel ATX vs PBO	<i>n</i> = 115	ODD: 100%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-ADHD-S scores with ATX 1.8 mg/kg (mean change from baseline $-1.2, P = 0.04$)
Kaplan, 2004 [39]	RCT – pooled ATX vs PBO	<i>n</i> = 98	ODD: 100%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-ADHD-S scores with ATX (mean change from baseline $-1.5±1.5$ vs $-0.7±1.1, P = 0.003$)

Citation	Study design	Number of patients	Comorbidities	Main findings for CGI for ADHD
Bangs, 2008 [30]	RCT – parallel ATX vs PBO	<i>n</i> = 226	ODD: 100%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-I (mean change from baseline 3.5±1.4 vs 3.9±1.0, <i>P</i> = 0.037) and CGI-S (mean change from baseline –0.7±1.4 vs –0.3±1.1, <i>P</i> = 0.013) scores with ATX
Dell'Agnello, 2009 [32]	RCT – parallel ATX vs PBO	<i>n</i> = 137	ODD: 100%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-ADHD-S scores with ATX (4.5±1.0 vs 5.2±1.0, <i>P</i> < 0.001)
Dittman, 2011 [33]	RCT – parallel ATX vs PBO	<i>n</i> = 180	ODD: 100%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-S scores with ATX (least squares mean treatment group difference –0.7 [95% CI: –1.1, –0.4], effect size –0.21, <i>P</i> < 0.001)
Connor, 2010 [31]	RCT – parallel GXR vs PBO	<i>n</i> = 217	ODD: 100%	NR
Tourette's disorder and other tic disorders				
Tourette's Syndrome Study Group, 2002 [40]	RCT – parallel MPHs vs CLON vs MPHs+CLON vs PBO	<i>n</i> = 136	Tourette: 94% Motor tic: 5% Vocal tic: 6% ODD: 38% [†]	<ul style="list-style-type: none"> CGI-ADHD-I response rate (investigator-rated) significantly higher for all treatment groups compared with PBO (MPHs: 80.6%, CLON: 60.6%, MPHs+CLON: 87.5%, PBO: 32.3%)
Allen, 2005 [28]	RCT – parallel ATX vs PBO	<i>n</i> = 148	Tourette: 79.1% Motor tic: 29.7% Vocal tic: 17.6% ODD: 21.6% [†]	<ul style="list-style-type: none"> Significantly greater improvements in CGI-ADHD/Psych-S (mean change from baseline –0.8±1.1, <i>P</i> < 0.001 vs –0.3±1.0, <i>P</i> = 0.008) and CGI-S scores (mean change from baseline –0.6±1.1, <i>P</i> < 0.001 vs –0.2±0.9, <i>P</i> = 0.054) with ATX
Scahill, 2001 [44]	RCT – parallel GXR vs PBO	<i>n</i> = 34	Tourette: 59.0% Motor tic: 35.3%	<ul style="list-style-type: none"> CGI-I response rate significantly higher with GXR (52.9% vs 0.0%), <i>P</i> < 0.001
Generalized anxiety disorder and major depressive disorder				
Geller, 2007 [34]	RCT – parallel ATX vs PBO	<i>n</i> = 113	Anxiety: 100%	<ul style="list-style-type: none"> Significantly greater improvements in CGI-S scores with ATX (mean change from baseline –0.9±1.2, <i>P</i> = 0.002)
Griffiths, 2018 [35]	RCT – crossover ATX vs PBO	<i>n</i> = 38	Anxiety: 100% ODD: 55.3% [†]	NR
Bangs, 2007 [29]	RCT – parallel ATX vs PBO	<i>n</i> = 142	MDD: 100%	<ul style="list-style-type: none"> CGI-I response rate significantly higher with ATX (47.8% vs 17.9%, <i>P</i> < 0.001) CGI-S response rate not significantly higher with ATX (18.8% vs 10.4%, <i>P</i> = 0.23)

[†]In addition to the comorbidity of interest and reported in ≥20% of patients.

ADHD, attention-deficit hyperactivity disorder; AMPs, amphetamine or a derivative; ATX, atomoxetine; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; CI, confidence interval; CLON, clonidine; GXR, guanfacine extended-release; MA, meta-analysis; MDD, major depressive disorder; MPHs, methylphenidate or a derivative; ODD, oppositional defiant disorder; OLE, open-label extension; PBO, placebo; PDD-NOS, pervasive developmental disorder-not otherwise specified; RCT, randomized controlled trial.

Additional file 1 Table S3 Main safety findings from meta-analyses and randomized controlled studies

Citation	Study design	Number of patients	Adverse events with significantly or clinically relevant higher frequency compared with PBO	Changes in weight	Changes in blood pressure	Other cardiovascular events
Autism spectrum disorder						
Reichow, 2013 [19]	MA – 3 trials[66, 84, 92] MPHs vs PBO	NR	Significantly greater risk of: Decreased appetite (ARD = 0.17 [95% CI: 0.03, 0.31]; NNH = 5.9 [95% CI: 3.2, 33.3]) Insomnia (ARD = 0.19 [95% CI: 0.02, 0.36]; NNH = 5.3 [95% CI: 2.8, 5.0]) Depressive symptoms (ARD = 0.07 [95% CI: 0.004, 0.13]; NNH = 14.3 [95% CI: 7.7, 250]) Irritability (ARD = 0.14 [95% CI: 0.05, 0.24]; NNH = 7.1 [95% CI: 4.2, 20]) Social withdrawal (ARD = 0.07 [95% CI: 0.002, 0.15]; NNH = 14.3 [95% CI: 6.7, 500])	NR	NR	NR
Pearson, 2013 [43]	RCT – crossover MPHs 0.21, 0.35, 0.48 mg/kg PBO	<i>n</i> = 24	Appetite loss (29–38%) Trouble sleeping (29–50%)	<ul style="list-style-type: none"> No significant changes in weight compared PBO 	<ul style="list-style-type: none"> No significant changes in blood pressure compared with PBO 	<ul style="list-style-type: none"> No significant changes in pulse rate compared with PBO
Kim, 2017 [70]	RCT – parallel MPHs 0.3 mg/kg MPHs 0.6 mg/kg	<i>n</i> = 9 <i>n</i> = 18	No dose-related increase in severe AEs (RISC-K) No suicidal behavior (C-SSRS)	<ul style="list-style-type: none"> No significant or clinically relevant changes in either group 	<ul style="list-style-type: none"> No significant or clinically relevant changes in either group 	<ul style="list-style-type: none"> No significant or clinically relevant changes in either group
Handen, 2000 [66]	RCT – crossover MPHs 0.3 mg/kg MPHs 0.6 mg/kg PBO	<i>n</i> = 13	≥5% increase in frequency (significance NR) Sad, unhappy, depressed (45.5%, 70%) Irritable, crabby, touchy, whiny (54.5%, 70%) Poor appetite (72.7%, 70%) Drowsy, dull, not alert (45.5%, 40%) Difficulty falling asleep 10.6–18.2% (all doses)	NR	NR	NR
RUPP, 2005 [84]	RCT – crossover MPHs 2.5–5 mg/kg MPHs 2.5–10 mg/kg MPHs 5–20 mg/kg vs PBO	RCT, <i>n</i> = 66 OLE, <i>n</i> = 34	Decreased appetite 24.2–24% (med–high doses) Irritability 12.1% (med dose) Emotional outburst 13.6% (med dose)	NR	NR	NR
Patra, 2019 [18]	MA – 3 trials[36, 38, 50] ATX vs PBO	<i>n</i> = 241	Relative risk [95% CI] Nausea and vomiting 1.91 [1.24, 2.94] Decreased sleep 1.79 [1.19, 2.70] Decreased appetite 1.79 [1.17, 2.73]	NR	NR	NR
Harfterkamp, 2012[38] 2013 [67]	RCT – parallel ATX (1.2 mg/kg/day) vs PBO	RCT ATX, <i>n</i> = 48 PBO, <i>n</i> = 49 OLE, <i>n</i> = 88	RCT phase Decreased appetite 27.1% Early morning awakening 10.4% Nausea 29.2% OLE phase Most AEs during the first 8 weeks of treatment decreased in frequency during the following 20 weeks of treatment. There were significant decreases in fatigue (from 18.2% to 6.8%) and nausea (13.6% to 1.1%)	NR	NR	NR

Citation	Study design	Number of patients	Adverse events with significantly or clinically relevant higher frequency compared with PBO	Changes in weight	Changes in blood pressure	Other cardiovascular events
NCT00498173 [41]	RCT – parallel ATX vs PBO	ATX, <i>n</i> = 29 PBO, <i>n</i> = 31	≥5% increase in frequency (significance NR) Constipation 10.3% Decreased appetite 31.0% Difficulty falling asleep 20.7% Emotional outburst 17.2% Nasal congestion/cold 13.8% Restlessness/agitation 13.8% Sedation/drowsiness 27.6% Self-injurious behaviour 20.7% Stomach discomfort 13.8% Decreased appetite 47%	NR	NR	NR
Handen, 2015 [36]	RCT – parallel ATX (1.8 mg/kg/day) vs PBO	<i>n</i> = 32 in each group (e.g., ATX, ATX+PT, PBO+PT, PBO)		NR	NR	NR
Arnold, 2006 [50]	RCT – crossover ATX (≤1.4 mg/kg/day) vs PBO	<i>n</i> = 16	Nausea/vomiting 31% Upset stomach 31% Fatigue 31% Racing heart 19% Appetite suppression 38%	• No significant differences between groups	• No significant differences between groups	• Significantly higher heart rate with ATX
Handen, 2008 [37]	RCT – crossover GXR (≤3 mg/day) vs PBO	<i>n</i> = 11	No significant differences in frequency or severity of pooled adverse effects	NR	• No significant differences between groups (<i>n</i> = 6)	• No significant differences in pulse rate between groups (<i>n</i> = 6)
Scahill, 2015 [45]	RCT – parallel GXR (≤4 mg/day) vs PBO	GXR, <i>n</i> = 30 PBO, <i>n</i> = 32	Anxiety 30% Decreased appetite 43.3% Drowsiness 86.7% Dry mouth 40% Emotional/tearful 40% Irritability 36.7% Fatigue 63.3% Mid-sleep awakening 30%	NR	• Frequency of decreased blood pressure significantly higher with GXR (53.3% vs 28.1%)	• Frequency of sinus bradycardia higher with GXR • Mean decrease in pulse rate higher with GXR

Oppositional defiant disorder

Spencer, 2006 [46]	RCT – parallel AMPs (10, 20, 30, or 40 mg/day) PBO	<i>n</i> = 308	≥5% increase in frequency (significance NR) Anorexia/decreased appetite 16.7–37.9% Abdominal pain 10.3–14.5% Emotional lability 3.3–8.7% Headache 26.2% – highest dose only Insomnia 13.3–27.9% Nervousness 5.0–8.2% Pharyngitis 2.9–11.5% Weight loss 3.3–14.8%	• Significant decrease in weight with AMPs	• No clinically relevant changes	• No clinically relevant changes in ECG measurements
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Citation	Study design	Number of patients	Adverse events with significantly or clinically relevant higher frequency compared with PBO	Changes in weight	Changes in blood pressure	Other cardiovascular events
Jahangard, 2017 [68]	RCT – parallel MPHs vs MPHs+risperidone	<i>n</i> = 84	NR	<ul style="list-style-type: none"> Significant changes in weight over time (5.7% increase with MPHs+risperidone, 2.4% decrease with MPHs) 	<ul style="list-style-type: none"> No significant differences between groups (significant increase in both groups) 	<ul style="list-style-type: none"> No significant differences in pulse rate between groups (significant increase in both groups)
Kolko, 1999 [72]	RCT – crossover MPHs (0.3 or 0.6 mg/kg) vs PBO	<i>n</i> = 20	Stimulant Drug Side Effects Rating Scale: No significant differences in the frequency or severity of side-effect symptoms between MPHs and PBO	NR	NR	NR
Klorman, 1990 [71]	RCT – crossover MPHs vs PBO	<i>n</i> = 48	Decreased appetite 29.8% Dry mouth 19.1% Shakiness 8.5%	<ul style="list-style-type: none"> Significant decrease in weight (<i>P</i> < 0.05) 	NR	NR
Connor, 2000 [55]	RCT – parallel MPHs (≤40 mg/day) CLON (≤0.3 mg/day) MPHs+CLON	<i>n</i> = 8 in each group	Severity of side effects decreased over time in all groups	<ul style="list-style-type: none"> No significant differences in weight over time in either group 	NR	<ul style="list-style-type: none"> No significant differences in pulse rate over time in either group
Garg, 2015 [63]	RCT – parallel MPHs vs PBO	MPHs, <i>n</i> = 15 ATX, <i>n</i> = 22	No significant differences between groups	NR	NR	NR
Kaplan, 2004 [39]	RCT – pooled ATX (≤2 mg/kg) vs PBO	ATX, <i>n</i> = 53 PBO, <i>n</i> = 45	Decreased appetite 18.9% Emotional lability 11.3%	NR	NR	NR
Bangs, 2008 [30]	RCT – parallel ATX vs PBO RCT ≤1.2 mg/kg/day OLE ≤1.4 mg/kg/day	ATX, <i>n</i> = 156 PBO, <i>n</i> = 70	Decreased appetite 24.4% Nausea 20.5% Fatigue 17.3%	<ul style="list-style-type: none"> Rates of weight decrease significantly higher with ATX (change from baseline: 3.5% vs 2.9%) 	<ul style="list-style-type: none"> Frequency of clinically significant blood pressure increase significantly higher with ATX (9.7% vs 1.6%) 	NR
Dell'Agnello, 2009 [32]	RCT – parallel ATX (1.2 mg/day) vs PBO	ATX, <i>n</i> = 105 PBO, <i>n</i> = 32	Anorexia 33.6% Nausea 20.6% Somnolence 29.9%	<ul style="list-style-type: none"> Significantly greater decrease in weight with ATX 	<ul style="list-style-type: none"> No significant differences in blood pressure 	<ul style="list-style-type: none"> No significant differences in heart rate
Dittman, 2011 [33]	RCT – parallel ATX (fast and slow titration, max dose 1.2 mg/kg/day) vs PBO	ATX, <i>n</i> = 121 PBO, <i>n</i> = 59	≥5% increase in frequency (significance NR) for fast/slow ATX titration Abdominal pain upper 15.0%/13.1% Anorexia 15.0%/11.5% Fatigue 35.0%/21.3% Headache 25.0%/14.8% Nausea 21.7%/19.7% Vomiting 15.0%/18.0%	NR	NR	NR

Citation	Study design	Number of patients	Adverse events with significantly or clinically relevant higher frequency compared with PBO	Changes in weight	Changes in blood pressure	Other cardiovascular events
Connor, 2010 [31]	RCT – parallel GXR (1–4 mg/day) vs PBO	GXR, <i>n</i> = 138 PBO, <i>n</i> = 79	≥5% increase in frequency (significance NR) Abdominal pain upper 11.8% Fatigue 11.0% Headache 22.1% Irritability 7.4% Sedation 13.2% Somnolence 50.7%	NR	<ul style="list-style-type: none"> Frequency of clinically significant blood pressure decrease higher with ATX (5.9% vs 1.3%) 	<ul style="list-style-type: none"> Greater decreases in heart rate with GXR Frequency of decreased heart rate (<50 bpm) was higher with GXR (5.1% vs 1.3%) No patients on GXR had QTcF or QTcB >500 msec or increase from BL ≥60 msec
Tourette's disorder and other tic disorders						
Gadow, 2007 [61] Gadow, 2011 [60] Gadow, 1999 [62]	RCT – crossover + OLE MPHs (0.1, 0.3, 0.5 mg/kg) vs PBO	RCT <i>n</i> = 71 OLE <i>n</i> = 34	NR	<ul style="list-style-type: none"> RCT: 6 wk Significant decrease in weight with increasing dose OLE: 2 y No significant or clinically relevant differences in expected vs actual weight gain (difference: 0.72 kg) 	<ul style="list-style-type: none"> RCT: 6 wk Significant increase in diastolic blood pressure with increasing dose OLE: 2 y Significant change in systolic (+6 mmHg) but not diastolic (–3 mmHg) blood pressure Not considered clinically relevant 	<ul style="list-style-type: none"> RCT: 6 wk Significant increase in heart rate with increasing dose OLE: 2 y Significant increase in heart rate (~10 bpm) Not considered clinically relevant
Castellanos, 1997 [52]	RCT – crossover MPHs vs AMPs vs PBO	<i>n</i> = 20	Decreased appetite with transient weight loss (MPHs 15%, AMPs 20%) Insomnia (MPHs 10%, AMPs 50%, PBO 5%) Transient obsessive-compulsive symptoms (MPHs 25%, AMPs 5%)	NR	NR	NR
Bloch, 2009 [16]	MA – 4 trials[40, 52, 61] MPHs vs PBO	<i>n</i> = 191	No difference in tic severity; noted that AEs were not well described in the included studies	NR	NR	NR
Law, 1999 [76]	RCT – parallel MPHs (0.7 mg/kg BID) vs PBO	MPHs, <i>n</i> = 46 PBO, <i>n</i> = 45	Target dose of 0.7 mg/kg MPHs not reached because of adverse effects at doses >0.5 mg/kg Onset of new clinically significant tics in patients without pre-existing tics: MPHs 19.6% vs PBO 16.7%, not significant Worsening of pre-existing tics: MPHs 33%, PBO 33%	NR	NR	NR

Citation	Study design	Number of patients	Adverse events with significantly or clinically relevant higher frequency compared with PBO	Changes in weight	Changes in blood pressure	Other cardiovascular events
Tourette's Syndrome Study Group, 2002 [40]	RCT – parallel MPHs, CLON, vs PBO	MPHs, <i>n</i> = 37 CLON, <i>n</i> = 34 PBO, <i>n</i> = 32	Significant differences NR (sedation higher vs PBO) MPHs+CLON 48%, MPHs 14%, PBO 6% Worsening of tics: MPHs 20%, CLON 26%, PBO 22% Tics limited dose increases: MPHs 35%, CLON 18%, PBO 19% Decreased appetite 15.8% Nausea 15.8%	NR	NR	NR
Allen, 2005 [28]	RCT – parallel ATX (≤ 1.5 mg/kg/day) vs PBO	ATX, <i>n</i> = 76 PBO, <i>n</i> = 72	Decreased appetite 15.8% Nausea 15.8%	<ul style="list-style-type: none"> Significant decrease in body weight with ATX Frequency of treatment-emergent weight loss ($\geq 3.5\%$) higher with ATX (53.3% vs 12.9%, $P < 0.001$) Frequency of weight loss as an AE was higher with ATX (2.6% vs 0.0%) 	NR	<ul style="list-style-type: none"> Significant increase in heart rate with ATX compared with a decrease with PBO Frequency of treatment-emergent increases in heart rate higher with ATX (13.3% vs 2.9%, $P = 0.032$) Significant decrease in QT interval (Fridericia's corrected) with ATX compared with a slight increase with PBO
Scahill, 2001 [44]	RCT – parallel GXR (≤ 4 mg/day) vs PBO	GXR, <i>n</i> = 17 PBO, <i>n</i> = 17	NR	<ul style="list-style-type: none"> No significant differences in weight change between groups 	<ul style="list-style-type: none"> No clinically relevant differences in blood pressure between groups 	<ul style="list-style-type: none"> No clinically relevant differences in pulse rate between groups
Generalized anxiety disorder and/or major depressive disorder						
Abikoff, 2005 [48]	RCT – parallel MPHs vs MPHs+fluvoxamine	MPHs, <i>n</i> = 8 MPHs +fluvoxamine, <i>n</i> = 12	No significant differences between groups	NR	NR	NR
Diamond, 1999 [56]	RCT – parallel MPHs (0.7 mg/kg) vs PBO	<i>n</i> = 91 +anxiety <i>n</i> = 19 for each group -anxiety MPHs, <i>n</i> = 27 PBO, <i>n</i> = 26	Side effects were grouped: affective, overfocusing, physiological, tics There were no differences between patients with and without comorbid anxiety for the difference in side effects between MPHs and PBO	NR	NR	NR
Geller, 2007 [34]	RCT – parallel ATX (≤ 1.8 mg/kg/day) vs PBO	ATX, <i>n</i> = 87 PBO, <i>n</i> = 89	Decreased appetite 14.3%	<ul style="list-style-type: none"> Significant decrease in body weight with ATX compared with an increase with PBO 	NR	<ul style="list-style-type: none"> Significant increase in heart rate with ATX compared with a decrease with PBO

Citation	Study design	Number of patients	Adverse events with significantly or clinically relevant higher frequency compared with PBO	Changes in weight	Changes in blood pressure	Other cardiovascular events
Kratochvil, 2005 [73]	RCT – parallel ATX vs ATX+fluoxetine	ATX, <i>n</i> = 46 ATX+fluoxetine, <i>n</i> = 127	No significant differences for ATX vs ATX+fluoxetine	<ul style="list-style-type: none"> Greater weight loss with ATX+fluoxetine 	<ul style="list-style-type: none"> Frequency of marked, sustained increases in blood pressure higher with ATX+fluoxetine 	<ul style="list-style-type: none"> Increase in heart rate higher with ATX+fluoxetine
Bangs, 2007 [29]	RCT – parallel ATX (≤ 1.8 mg/kg/day) vs PBO	ATX, <i>n</i> = 72 PBO, <i>n</i> = 70	Decreased appetite 12.5% Nausea 22.2%	<ul style="list-style-type: none"> Significant decrease in body weight with ATX compared with an increase with PBO Frequency of weight loss as an AE higher with ATX (8.3% vs 1.4%) 	<ul style="list-style-type: none"> No significant differences between groups At endpoint of OLE, diastolic blood pressure ($+2.5 \pm 10.2$ mmHg, <i>n</i> = 118, <i>P</i> = 0.005) was elevated relative to the start of the OLE in the ATX group 	<ul style="list-style-type: none"> During acute treatment, significant increases in heart rate and decreases in ECG RR and PR intervals with ATX vs PBO During OLE, significant increases in heart rate and decreases in ECG RR interval with ATX vs PBO

AE, adverse event; AMPs, amphetamine or a derivative; ARD, absolute risk difference; ATX, atomoxetine; BID, twice daily; bpm, beats per minute; BL, baseline; CI, confidence interval; CLON, clonidine; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ER, extended release; GXR, guanfacine extended-release; MA, meta-analysis; MPHs, methylphenidate or a derivative; NR, not reported; OLE, open-label extension; PR, pulse rate; NNH, number needed to harm; PBO, placebo; PT, parent training; RCT, randomized controlled trial; RISC-K, Response Impressions and Side Effects Checklist-Kids.

Additional file 1 Table S4 Summary of findings for changes in body weight, blood pressure, and pulse rate or heart rate compared with placebo during active treatment for ADHD symptoms in randomized controlled trials

	Citation	Treatment	Body weight [†]	Blood pressure [†]	HR/PR [†]
Autism spectrum disorder	No studies	AMPs	None	None	None
	Pearson, 2013 [43]	MPHs	No significant differences	No significant differences	No significant differences
	Arnold, 2006 [50]	ATX	No significant differences	No significant differences	Higher HR
	Scahill, 2015 [45] [‡]	GXR	None	Lower	Lower PR
Oppositional defiant disorder	Spencer, 2006 [46]	AMPs	Lower	No clinically relevant differences	No clinically relevant differences
	Klorman, 1990 [71]	MPHs	Lower	None	None
	Bangs, 2008 [30] Dell'Agnello, 2009 [32]	ATX	Lower	Higher systolic No differences	No significant differences
	Connor, 2010 [31]	GXR	None	Lower	Lower HR/PR
Tourette's disorder, other tic disorders	No studies	AMPs	None	None	None
	Gadow, 2007 [61]	MPHs	Lower (dose-related)	Higher diastolic (dose-related)	High HR (dose-related)
	Allen, 2005 [28]	ATX	Lower	NR	Higher HR
	Scahill, 2001 [44]	GXR	No significant differences	No clinically relevant differences	No clinically relevant differences
Generalized anxiety disorder and/or MDD	No studies	AMPs	None	None	None
	No studies [§]	MPHs	None	None	None
	Geller, 2007 [34] Bangs, 2007 [29]	ATX	Lower	No significant differences	Higher HR
	None	GXR	None	None	None

[†]Statistically significant or clinically relevant differences compared with placebo.

[‡]Handen, 2008 [37] is not included because the analysis included a subgroup of 6 patients only.

[§]Gadow, 2011 [60] is not included because it was a subgroup analysis.

ADHD, attention-deficit hyperactivity disorder; AMPs, amphetamine or a derivative; ATX, atomoxetine; GXR, guanfacine extended-release; HR, heart rate; MDD, major depressive disorder; MPHs, methylphenidate or a derivative; NR, not reported; PR, pulse rate.