Pharmacological and nonpharmacological interventions for children with attention-deficit hyperactivity disorder (ADHD)

Q7: What is the effectiveness, safety and role of pharmacological and non-pharmacological interventions, within non-specialist health care for children with a diagnosis of Attention-deficit hyperactivity disorder (ADHD)?

Background

Attention-deficit hyperactivity disorder (ADHD) is presumably a common but highly treatable mental disorder. Long-term consequences relate to reports of poorer occupational attainment, and increased co-morbid psychiatric illness and substance use disorders. There are both pharmacological and non-pharmacological treatments. Stimulants are being used widely despite concerns about their side effects and potentials for abuse. It is not yet clears to what extent non-specialized health care providers can be able to mange this disorder and whether the new stimulants are superior to methylphenidate in terms of efficacy and side effects.

Population/Intervention(s)/Comparator/Outcome(s) (PICO)

Population:	children with a diagnosis of ADHD
Interventions:	pharmacological interventions (atomoxetine, methylphenidate, dexamphetamine)
Comparator:	placebo
	One intervention versus other
Outcomes:	symptom reduction
	adverse effects
	family/school functioning
	treatment satisfaction
	physical health

user satisfaction

List of the systematic reviews identified by the search process

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews
I	**Atomoxetine vs. Placebo**	Symptom reduction (efficacy)	-Keen & Hadijikoumi (2008) -NICE (2009) -King et al (2006) -Cheng et al (2007)
		Safety/Harm: Narrative & Quantitative	- NICE (2009) -King et al (2006) -Cheng et al (2007)
		Family/School Functioning	-NICE (2009) -King et al (2008) -Cheng et al (2007) - Spencer et al (2005)
		Treatment satisfaction	NICE (2009)
		Physical Health	No systematic reviews
		User Satisfaction	No systematic reviews
II	**Methylphenidate vs. Placebo**	Symptom reduction (efficacy)	-NICE (2009) -King et al (2006) -Keen & Hadijikoumi (2008)
		Safety/Harm: Narrative & Quantitative	-NICE (2009) -Schachter et al (2001) -King et al (2006) -Smith et al (2000)

		Family/School Functioning	Conduct Problems: NICE (2009)
		Treatment satisfaction	NICE (2009)
		Physical Health	
		User Satisfaction	
III	**Amphetamines (mainly Dexamphetamine) vs. Placebo**	Symptom reduction (efficacy)	-King et al (2006) Keen & Hadijikoumi (2008)
		Safety/Harm: Narrative & Quantitative	-King et al (2006)
		Family/School Functioning	
		Treatment satisfaction	
		Physical Health	
		User Satisfaction	
IV.	**Methylphenidate versus atomoxetine**	For drugs supported by the evidence	NICE (2009) Keen & Hadijikoumi (2008)

Narrative description of the studies that went into the analysis:

ATOMOXETINE VERSUS PLACEBO

According to Appendix 17.5 of NICE (2009), a total of 11 trials compared atomoxetine with placebo (1241 children randomized to atomoxetine and 756 randomized to placebo). All included studies were double-blind, patient age ranged between 6-18 years, and recruitment occurred in outpatients or inpatients investigative/academic sites in most studies. Atomoxetine mean dose ranged from 0.5 mg/kg/day to 2.0 mg/kg/day. Length of follow-up ranged between 42 and 238 days.

Study by study table:

	DB	Setting	Follow-up	Ato/Plo	Age range
Allen et al	Yes	Hospital	140 days	76/72	7-17 years

(2005) (ADHD and Tic disorder)				Mean dose = 1.33mg/kg/day	
Bohnsted et al (2005)	Yes	Outpatient clinic	49 days	10/6 1.2 mg/kg/day (max: 1.8)	8-11
Brown et al (2006)	Yes	PHC, mental health professionals, advertisement	49 days	101/52 1.32 mg/kg/day	8-12
Kelsey et al (2004)	Yes	Outpatients	56 days	133/64 Max 1.8 mg/kg/day	6-12
Michelson et al (2001)	Yes	Outpatients	56 days	Ato0.5 mg/kg/day Ato1.8 mg/kg/day Ato1.2 PLO 44/85/84/84	8-18
Michelson et al (2002)	Yes	Outpatients	42	85/86 1.0 mg/kg/day	6-16
Michelson et al (2004)	Yes	Academic sites	238	292/124 1.2-1.8 mg/kg/day	6-15
Spencer et al (2002a)	Yes	Academic sites	63	65/62 2.0 mg/kg/day	7-12
Spencer et al (2002b)	Yes	Academic sites	63	64/62 2.0 mg/kg/day	7-12
Weiss et al (2005)	Yes	Investigative sites	49	101/52 1.2 mg/kg/day (max: 1.8 mg/kg/day)	8-12
Wernicke et al	Yes	Outpatients	63	101/92	7-12

(2004a)				2.0 mg/kg/day (max)	

METHYLPHENIDATE VERSUS PLACEBO

According to Appendix 17.5 of NICE (2009), a total of 14 trials compared methylphenidate with placebo (1100 children randomized to methylphenidate and 670 randomized to placebo). All included studies were double-blind, patient age ranged between 6-18 years, and recruitment occurred in outpatients or inpatients investigative/academic sites in most studies. Methylphenidate mean dose ranged from 10 to 60 mg /day. Length of follow-up ranged between 7 and 197 days.

Study by study table:

	DB	Setting	Follow-up	MTP/Plo	Age range
Butter 1983	Yes		7	10/10 10-20mg/day	6-12
Conners 1980	Yes		56	20/21 Max 60mg/day	6-11
Findling et al (2006)	Yes		21	272/46	6-12
Gittelman-klein et al (1976a)	Yes		28	41/42 1.66mg/kg/day	6-12
Greenhill et al (2002)	Yes		21	158/163 40.7mg/day	6-16
Greenhill et al (2006)	Yes		49	53/50 Max: 30mg/day	6-17
Ialongo et al (1994)	Yes	Psychological clinic	98	32/16 0.4 to 0.8mg/kg/day	7-11
Kupietz et al (1988)	Yes	Child development centre, advertisements	197	42/16 0.3 to 0.7mg/kg/day	7-13
Kurlan et al (2002)	Yes		112	37/32 Max: 60mg/day	7-14
Lerer et al (1977)	Yes		28	25/25	8-12

				0.6-0.7mg/kg/day	
Pliszka et al (2000)	Yes	School children	21	20/18 Mean: 25.2mg/day	Mean age: 8
Wigal et al (2004)	Yes		28	90/42 Max: 20mg/day	6-17
Wilens et al (2006)	Yes		14	87/90 Max: 72mg/day	13-18
Wolraich et al (2001)	Yes	Advertisements	28	213/99 29-34mg/day	6-12

DEXAMPHETAMINE VERSUS PLACEBO

According to King et al (2006), a total of 6 trials compared dexamphetamine with placebo (143 children randomized to dexamphetamine and 135 randomized to placebo). All included studies were double-blind, patient age ranged between 4-12 years, and recruitment occurred in outpatients sites in most studies. Dexamphetamine mean dose ranged from 10 to 40 mg /day. Length of follow-up ranged between 8 weeks to 15 months.

Study by study table:

	DB	Setting	Follow-up	Dex/Plo	Age range
Arnold et al (1976)	Yes		12 weeks	31/31 Mean 21.75mg	4-12
Arnold et al (1989)	Yes		12 weeks	18/18 10-15mg/day	6-12
Conners et al (1972)	Yes		8 weeks	28/28 20-40mg/day	6-12
Conrad et al (1971)	Yes		4-6 months	17/18 10-20mg/day	4-6
Gillberg et al (1997)	Yes		15 months	32/30 17mg/day	6-11
Greenberg 1972	Yes		8 weeks	17/10 25mg/day	6-11

METHYLPHENIDATE VERSUS ATOMOXETINE

According to NICE (2009), only one study compared methylphenidate with placebo (Wang et al, 2007) (166 children randomized to methylphenidate and 164 randomized to atomoxetine). Patient age ranged between 6-16 years, and recruitment occurred in outpatients. Methylphenidate dose was 0.2-0.6mg/kg/day and atomoxetine dose was 0.8-1.8mg/kg/day. Length of follow-up was 8 weeks.

Study by study table:

	DB	Setting	Follow-up	MTP/Ato	Age range
Wang et al (2007)	Yes	Outpatients	8 weeks	166/164 MTP: 0.2-0.6mg/kg/day Ato: 0.8-1.8mg/kg/day	6-16

GRADE tables

Table 1

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-14
Question: Should atomoxetine vs. placebo be used for ADHD?[1]
Settings:
Bibliography: NICE (2009). Attention Deficit Hyperactivity Disorder. The NICE Guideline on Diagnosis and management of ADHD in children, young people and adults. Section 7.2.14 From evidence to recommendations: psychological interventions for children and young people with ADHD. In: NICE Technology Appraisal 72. London: National Institute for Health and Clinical Excellence;

Cheng JY et al (2007). Efficacy and safety of atomoxetine for attentiondeficit/hyperactivity disorder in children and adolescents-meta-analysis and metaregression analysis. *Psychopharmacology,* 194:197–209;

King S et al (2006). A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. *Health Technology Assessment,* 10:23;

Spencer TJ et al (2005). Effects of atomoxetine on growth after 2-year treatment among paediatric patients with attention deficit/hyperactivity disorder. *Paediatrics,* 116:e74–e80.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	atomoxetine	placebo	Relative (95% CI)	Absolute		
Symptom reduction (teacher-rating) (Better indicated by lower values)												
5[2]	randomized trials	serious[3]	serious[4]	no serious indirectness	no serious imprecision	reporting bias[5]	520	283	-	SMD 0.44 lower (0.7 to 0.19 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Symptom reduction (parent-rating) (Better indicated by lower values)												
10[6,7]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	945	693	-	SMD 0.58 lower (0.69 to 0.48 lower)	⨁⨁◯◯ MODERATE	IMPORTANT
No improvement												
3[8]	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	113/420 (26.9%)	131/248 (52.8%)	RR 0.57 (0.47 to 0.69)	227 fewer per 1000 (from 164 fewer to 280 fewer)	⨁◯◯◯ LOW	IMPORTANT
Functioning (Better indicated by higher values)												
3[9]	randomized trials	no serious limitations	no serious inconsistency	serious[10]	no serious imprecision	none	576	287	-	SMD 0.467 higher (0.249 to 0.685 higher)	⨁⨁◯◯ MODERATE	CRITICAL
Functioning (conduct problems) (Better indicated by lower values)												
2[11]	randomized trials	serious[3]	no serious inconsistency	serious[12]	no serious imprecision	none	374	206	-	SMD 0.31 lower (0.49 to 0.14 lower)	⨁◯◯◯ LOW	CRITICAL
Treatment acceptability (total dropouts)												
8[13]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	266/1117 (23.8%)	181/805 (22.5%)	RR 1.01 (0.75 to 1.37)[14]	2 more per 1000 (from 56 fewer to 83 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Anorexia												
4[15]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[16]	73/480 (15.2%)	14/276 (5.1%)	RR 3.04 (1.75 to 5.3)	103 more per 1000 (from 38 more to 218 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Emotional liability (proxy of suicide ideas)												
1[17]	randomized trials	no serious limitations	no serious inconsistency	serious[18]	very serious[19]	none	6/53 (11.3%)	0/45 (0%)	RR 11.07 (0.64 to 191.34)	0 more per 1000 (from 0 fewer to 0 more)	⨁◯◯◯ VERY LOW	CRITICAL
Weight (Better indicated by higher values)												
4[20]	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	601	381	-	SMD 1.11 lower (1.25 to 0.97 lower)[21]	⨁⨁⨁◯ MODERATE	CRITICAL
User satisfaction												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL

[1] According to Appendix 17.5 of NICE (2009), a total of 11 trials compared atomoxetine with placebo (1241 children randomized to atomoxetine and 756 randomized to placebo). All included studies were double-blind, patient age ranged between 6-18 years, and recruitment occurred in outpatients or inpatients investigative/academic sites in most studies. Atomoxetine mean dose ranged from 0.5 mg/kg/day to 2.0 mg/kg/day. Length of follow-up ranged between 42 to 238 days.

[2] Page 28 of Appendix 18.1 of NICE (2009).

[3] One included study (Michelson 2004) has more than 30% of dropouts plus dropouts are not equally distributed.

[4] Heterogeneity exceeds 50% (I-squared=60.2%).

[5] This outcome is the primary outcome in the included clinical trials. In this comparison (drug versus placebo) and in this condition (ADHD) it is likely that trials showing a positive effect in terms of primary outcome were more likely to be published than trials showing no effect. So publication bias might have occurred, and unpublished trials were not included.

[6] Page 29 of Appendix 18.1 of NICE (2009).

[7] One additional trial (Allen 2005) included patients with ADHD and Tic Disorder. It found that atomoxetine was more effective than placebo in terms of symptom reduction (parent rating): Fixed effect SMD = -0.56 (95% CI -0.89 to -0.23) (sample size = 145 patients). [Page 72 of Appendix 18.1 of NICE SR].

[8] Page 32 of Appendix 18.1 of NICE (2009).

[9] Page 200 of Cheng 2007.

[10] the Child Health Questionnaire (CHQ) is a surrogate measure of functioning.

[11] Page 31 of Appendix 18.1 of NICE (2009) (Michelson 2001 was considered once)

[12] Conduct problems is a surrogate outcome compared with overall functioning.

[13] Page 42 and 43 of Appendix 18.1 of NICE (2009) (Michelson2001a,b,c was considered once).

[14] Our re-analysis of data reported in NICE (2009). 11 studies were included but one had no dropouts so only 10 studies (and 8 comparisons because Michelson2001a,b,c was considered once) contributed to the overall estimate.

[15] Page 34 onwards of Appendix 18.1 of NICE (2009).

[16] Only four studies reported this outcome measure.

[17] Page 41 of Appendix 18.1 of NICE (2009).
[18] Emotional liability is a surrogate outcome compared with completed suicide.
[19] Only one trial with less than 100 patients, plus the 95% confidence interval includes no effect ranging from appreciable benefit to appreciable harm.
[20] Page 64, figure 19 of King 2006. There in one additional study (Spencer 2005) that pooled data from 13 multicentre trials conducted at 90 sites across North America. No systematic review was performed. Included trials were selected on the basis of being part of the clinical development of atomoxetine in paediatric populations. Data were analysed on weight and height for patients who completed at least two years of treatment with atomoxetine (patients randomly assigned to placebo were not included in the analysis and a pre-post design was employed). A total of 412 patients aged between 6 and 16 years received atomoxetine treatment (maximal dose: 1.8 mg/Kg per day) for at least two years. The analysis found that, after two years, observed weight and height were close to those predicted on the basis of the patients' baseline weight and height. Weight increased an average of 10.8 Kg, a decrease relative to baseline normative weight of 2.7 percentiles, corresponding to 0.87 Kg. Height increased an average of 13.3 cm, a decrease relative to baseline normative height of 2.2 percentiles, corresponding to 0.44 cm. These findings suggest that, at a group level, there was only a minimal effect on weight and height.
[21] Our re-analysis of data extracted from Figure 19 of King 2006.

Table 2

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-15
Question: Should methylphenidate vs. placebo be used for ADHD?[1]
Settings:
Bibliography: NICE (2009). Attention Deficit Hyperactivity Disorder. The NICE Guideline on Diagnosis and management of ADHD in children, young people and adults. Section 7.2.14 From evidence to recommendations: psychological interventions for children and young people with ADHD. In: NICE Technology Appraisal 72. London: National Institute for Health and Clinical Excellence;

King S et al (2006). A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. *Health Technology Assessment,* 10:23.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	methylphenidate	placebo	Relative (95% CI)	Absolute		
Symptom reduction(teacher-rated) (Better indicated by lower values)												
5[2,3,4]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	333	255	-	SMD 0.48 lower (1.06 to 0.62 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Symptom reduction(parent-rated) (Better indicated by lower values)												
4[6,7]	randomized trials	no serious limitations	serious[8]	no serious indirectness	no serious imprecision	reporting bias[5]	314	238	-	SMD 0.79 lower (1.14 to 0.45 lower)	⨁⨁◯◯ LOW	IMPORTANT

No improvement												
7[9]	randomized trials	no serious limitations	very serious[10]	no serious indirectness	no serious imprecision	reporting bias[5]	180/380 (47.4%)	208/295 (70.5%)	RR 0.57 (0.42 to 0.78)	303 fewer per 1000 (from 155 fewer to 409 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Functioning (conduct problems, teacher rating) (Better indicated by lower values)												
4[11,12]	randomized trials	no serious limitations	no serious inconsistency	serious[13]	no serious imprecision	none	175	92	-	SMD 0.58 lower (0.84 to 0.31 lower)	⨁⨁◯◯ MODERATE	CRITICAL
Treatment acceptability (total dropouts)												
8[14]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/484 (13%)	109/488 (22.3%)	RR 0.58 (0.44 to 0.77)	94 fewer per 1000 (from 51 fewer to 125 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Anorexia												
4[15]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[16]	27/315 (8.6%)	10/319 (3.1%)	RR 2.69 (1.39 to 5.24)	53 more per 1000 (from 12 more to 133 more)	⨁⨁◯◯ MODERATE	CRITICAL
Weight (Better indicated by higher values)												
1[17]	randomized trials	no serious limitations	no serious inconsistency	serious[18]	very serious[19]	none	20[20]	18[20]	-	MD 0.70 lower (6.16 lower to 4.76 higher)	⨁◯◯◯ VERY LOW	CRITICAL
User satisfaction												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL

[1] According to Appendix 17.5 of NICE (2009), a total of 14 trials compared methylphenidate with placebo (1100 children randomized to methylphenidate and 670 randomized to placebo). All included studies were double-blind, patient age ranged between 6-18 years, and recruitment occurred in outpatients or inpatients investigative/academic sites in most studies. Methylphenidate mean dose ranged from 10 to 60 mg /day. Length of follow-up ranged between 7 and 197 days.

[2] Page 4 of Appendix 18.1 of NICE (2009).

[3] Two additional studies were included in NICE (2009) but considered in separate analyses. The first study (Butter1983), which employed a low dose of methylphenidate versus placebo, showed a non-significant advantage of methylphenidate in terms of SMD (-0.79, 95% CI -1.70 to 0.13, sample size = 20). The second study (Kurlan2002), which did not report the mean values at endpoint, showed a positive effect of methylphenidate over placebo (SMD -1.69, 95% CI -2.24 to -1.14, sample size = 70).

[4] One additional study (Kupietz1988) included children with ADHD and developmental reading disorder (page 70 of Appendix 18.1 of NICE (2009)). It found that, in comparison with placebo, both low (SMD -1.61, 95% CI -2.69 to -0.53, sample size 19) and medium (SMD -1.35, 95% CI -2.29 to -0.40, sample size 22) dose of methylphenidate were better than placebo.

[5] This outcome is the primary outcome in the included clinical trials. In this comparison (drug versus placebo) and in this condition (ADHD) it is likely that trials showing a positive effect in terms of primary outcome were more likely to be published than trials showing no effect. So publication bias might have occurred, and unpublished trials were not included.

[6] Page 5 of Appendix 18.1 of NICE (2009).
[7] Two additional studies were included in NICE (2009) but considered in a separate analysis (page 6 of Appendix 18.1 of NICE (2009)). Both studies (Lerer1977 and Kurland 2002) did not report the mean score at endpoint but reported the mean change score. Re-analysis of data extracted from these two studies showed a non-significant advantage of methylphenidate over placebo (SMD -1.34, 95% CI -3.26 to 0.58, sample size 205, I-squared 96.7%).
[8] Heterogeneity exceeds 50% (I-squared 59.6%) (some confidence intervals do not overlap).
[9] Page 9 of Appendix 18.1 of NICE (2009).
[10] Heterogeneity exceeds 80% (I-squared 82.5%).
[11] Page 7 of Appendix 18.1 of NICE (2009).
[12] There are 4 additional studies that reported data on conduct problems. One study (Ialongo1994) employed a low dose of methylphenidate versus placebo and showed a non-significant advantage of methylphenidate (SMD -0.43, 95% CI -1.13 to 0.27, sample size 32). A second study (Kurland2002), which did not report the mean score at endpoint but reported the mean change score, found a significant advantage of methylphenidate over placebo (SMD -1.21, 95% CI -1.72 to -0.71, sample size 71). The last two studies assessed conduct problems as reported by parents. They found a significant advantage of methylphenidate over placebo (SMD -0.73, 95% CI -1.06 to -0.41, sample size 199).
[13] Conduct problems is a surrogate outcome compared with overall functioning.
[14] Our re-analysis of dropouts due to any reason as reported at page 16 and 17 of Appendix 18.1 of NICE (2009).
[15] Page 12 of Appendix 18.1 of NICE (2009).
[16] Only four studies reported this outcome measure.
[17] Page 27 of King 2006.
[18] Only one study contributed to this outcome so we have doubts about applicability of study findings.
[19] The study mentioned in King 2006 randomly assigned less than 100 children (sample size = 58) with ADHD, Additionally, the 95% confidence interval includes no effect ranging from appreciable benefit to appreciable harm.
[20] Page 31 of Appendix 17.5 of NICE (2009).

Table 3

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-15
Question: Should dexamphetamine vs. placebo be used for ADHD?[1]
Settings:
Bibliography: King S et al (2006). A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. *Health Technology Assessment,* 10:23; Keen D, Hadijikoumi I (2008). ADHD in children and adolescents. *BMJ Clinical Evidence*, 10:312.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	dexamphatamine	placebo	Relative (95% CI)	Absolute		
Symptom reduction (Better indicated by lower values)												

6[2]	randomized trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	reporting bias[4]	0	0	-	not pooled[5]	⨁⨁⨁◯ LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
Treatment acceptability (total dropouts)												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
User satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL

[1] According to King 2006, a total of 6 trials compared dexamphetamine with placebo (143 children randomized to dexamphetamine and 135 randomized to placebo). All included studies were double-blind, patient age ranged between 4-12 years, and recruitment occurred in outpatients sites in most studies. Dexamphetamine mean dose ranged from 10 to 40 mg/day. Length of follow-up ranged between 8 weeks to 15 months.

[2] Page 53 onwards of King 2006 and page 6 of Keen & Hadijikoumi (2008).

[3] Although no formal test of heterogeneity was performed, qualitative analysis of outcomes revealed high levels of between-study heterogeneity (page 53 onwards of King 2006).

[4] This outcome is the primary outcome in the included clinical trials. In this comparison (drug versus placebo) and in this condition (ADHD) it is likely that trials showing a positive effect in terms of primary outcome were more likely to be published than trials showing no effect. So publication bias might have occurred, and unpublished trials were not included.

[5] King 2006 did not pool data from included trials. The first study (Gillberg 1997, sample size = 30) reported data in graph. Conners 1972 (sample size = 84) reported a significant difference between dexamphetamine and placebo only when using a symptom checklist, but not when using the parent questionnaire. Of the three studies that evaluated high dosages (above 20 mg/day) of dexamphetamine versus placebo, one (Arnold 1976, sample size = 31) reported that children in the dexamphetamine group had better scores than children in the placebo group (no statistical analysis performed). The remaining two studies (Conrad 1971, sample size = 81; Greenberg 1972, sample size = 61) did not score well in the quality assessment, and no reliable figures were extracted by King 2006. Finally, one study evaluated 10-15 mg/day time-release dexamphetamine administered once daily (Arnold 1989, sample size = 19). It found that dexamphetamine time-release capsules were significantly better than placebo.

Table 4

Author(s): Corrado Barbui, Taghi Yasamy

Date: 2009-04-21

Question: Should methylphenidate vs. atomoxetine be used for ADHD?[1]

Settings:

Bibliography: NICE (2009). Attention Deficit Hyperactivity Disorder. The NICE Guideline on Diagnosis and management of ADHD in children, young people and adults. Section 7.2.14 From evidence to recommendations: psychological interventions for children and young people with ADHD. In: NICE Technology Appraisal 72. London: National Institute for Health and Clinical Excellence.

Keen D, Hadijikoumi I (2008). ADHD in children and adolescents. *BMJ Clinical Evidence*, 10:312 .

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	methylphenidate	atomoxetine	Relative (95% CI)	Absolute		
Symptom reduction (parent-rating) (Better indicated by lower values)												
1[2]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[4]	164	162	-	SMD 0.05 lower (0.27 lower to 0.17 higher)	⨁⨁◯◯ LOW	IMPORTANT
Treatment acceptability (total dropouts)												
1[2]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[5]	14/166 (8.4%)	26/164 (15.9%)	RR 0.53 (0.28 to 0.98)	75 fewer per 1000 (from 3 fewer to 114 fewer)	⨁⨁◯◯ LOW	CRITICAL
Anorexia												
1[6]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[5]	42/166 (25.3%)	61/164 (37.2%)	RR 0.68 (0.49 to 0.94)	119 fewer per 1000 (from 22 fewer to 190 fewer)	⨁⨁◯◯ LOW	CRITICAL
Nausea												
1[6]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[5]	17/166 (10.2%)	33/164 (20.1%)	RR 0.50 (0.29 to 0.87)	101 fewer per 1000 (from 26 fewer to 143 fewer)	⨁⨁◯◯ LOW	CRITICAL
Decreased appetite												
1[6]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	serious[7]	reporting bias[5]	32/166 (19.3%)	46/164 (28%)	RR 0.68 (0.46 to 1.02)	90 fewer per 1000 (from 151 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia												
1[6]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	serious[7]	reporting bias[5]	9/166 (5.4%)	5/164 (3%)	RR 1.77 (0.6 to 5.19)	23 more per 1000 (from 12 fewer to 128 more)	⨁◯◯◯ VERY LOW	CRITICAL

[1] According to NICE (2009), only one study compared methylphenidate with placebo (Wang2007) (166 children randomized to methylphenidate and 164 randomized to atomoxetine). Patient age ranged between 6-16 years, and recruitment occurred in outpatients. Methylphenidate dose was 0.2-0.6mg/kg/day and atomoxetine dose was 0.8-1.8mg/kg/day. Length of follow-up was 8 weeks.
[2] Page 27 of Appendix 18.1 of NICE (2009) and Wang 2007 page 225 (Patient characteristics).
[3] Only one study contributed to this outcome so we have doubts about the applicability of study findings.
[4] No explanation was provided.
[5] One trial only.
[6] Page 5 of Keen & Hadijikoumi (2008).
[7] Although more than 100 patients were included, confidence interval is very wide and includes no effect.

Additional information that was not GRADEd (safety and tolerability issues)

- There is uncertainty on the balance of risks and benefits of long-term drug treatment in children with ADHD. Little empirical evidence is available to guide clinicians on questions such as the optimum duration of treatment, when it is appropriate to consider drug discontinuation and how and when to combine pharmacological and psychological treatments. Furthermore, the increasing use of stimulants in clinical practice has raised concerns about the potential for stimulant drug misuse and diversion (NICE (2009)).
- In the UK, methylphenidate and atomoxetine are licensed for the treatment of ADHD (hyperkinetic disorders) in children aged 6 years and older while dexamfetamine is licensed for children from age 3 years.
- According to the WHO Model List of Essential Medicines for Children (October 2007), no medicines are listed for ADHD (it is not mentioned)
- NICE (2009) (page 303): In school-age children and young people with severe ADHD, drug treatment should be offered as the first-line treatment. Drug treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis. Continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements. Where drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended.
- NICE (2009) (page 304 onwards): Before starting drug treatment, children and young people with ADHD should have a full pre-treatment assessment, which should include: ● full mental health and social assessment; ● full history and physical examination, including assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms, heart rate and blood pressure (plotted on a centile chart), height and weight (plotted on a growth chart), family history of cardiac disease and examination of the cardiovascular system; ● an electrocardiogram (ECG) if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination; ● risk assessment for substance misuse and drug diversion (where the drug is passed on to others for non-prescription use).

ATOMOXETINE:

Safety table	**Source document**
Frequent adverse events:	

Abdominal pain, nausea and vomiting, decreased appetite with associated weight loss, dizziness and slight increases in heart rate and blood pressure	Page 258 of NICE (2009)
Rare adverse events: Liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice. Toxic psychotic symptoms, specifically involving visual and tactile hallucinations of insects	Page 258 of NICE (2009) Page 5 of Keen & Hadijikoumi (2008)
Abuse liability: Atomoxetine has less potential for misuse compared with stimulants and does not require the same strict prescribing and storage conditions as methylphenidate and dexamphetamine	Page 258 of NICE (2009)
Other safety concerns: Suicide-related behavior (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. The rate of sudden death with atomoxetine has been estimated as 0.5 per 100,000 patient-years, which is not clinically different from the rate for other CNS stimulants, and is not in excess of the baseline rate of sudden death in the paediatric population (estimated to be 1.3–1.85/100,000).	Page 259 of NICE (2009) Page 5 of Keen & Hadijikoumi (2008)

METHYLPHENIDATE:

Safety table	**Source document**
Frequent adverse events: Decreased appetite, sleep disturbance, headaches, stomach aches, drowsiness, irritability, tearfulness, mildly increased blood pressure and pulse. Decrease in appetite can lead to a decrease in expected growth during the active period of drug treatment There is controversy regarding the association of methylphenidate and tics	Page 235 of NICE (2009) Page 236 of NICE (2009) Page 236 of NICE (2009)
Rare adverse events: Psychotic symptoms and sensitivity reactions.	Page 235 of NICE

	(2009)
Abuse liability: Stimulants are controlled drugs and have the potential for misuse and diversion, either for subjective effects or for effects on performance	Page 252 of NICE (2009)
Other safety concerns: Suicide-related behavior (suicide attempts and suicidal ideation) has been reported in patients treated with methylphenidate. The rate of sudden death with CNS stimulant and atomoxetine has been estimated, per 100,000 patient-years, as 0.2 for methylphenidate, 0.3 for amphetamine, and 0.5 for atomoxetine. The differences are not in excess of the baseline rate of sudden death in the paediatric population, which is estimated to be 1.3–1.85/100,000.	Page 10 of Keen & Hadijikoumi (2008) Page 10 of Keen & Hadijikoumi (2008)

DEXAMPHETAMINE:

Safety table	**Source document**
Frequent adverse events: Decreased appetite, weight loss, sleep disturbance, dry mouth, thirst.	Page 256 of NICE (2009)
Rare adverse events: Psychotic symptoms.	Page 256 of NICE (2009)
Abuse liability: Stimulants are controlled drugs and have the potential for misuse and diversion, either for subjective effects or for effects on performance	Page 252 of NICE (2009)
Other safety concerns: The rate of sudden death with CNS stimulant and atomoxetine has been estimated, per 100,000 patient-years, as 0.2 for methylphenidate, 0.3 for amphetamine, and 0.5 for atomoxetine. The differences are not in excess of the baseline rate of sudden death in the paediatric population, which is estimated to be 1.3–1.85/100,000.	Page 10 of Keen & Hadijikoumi (2008)

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From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	A total of 11 short-term trials compared atomoxetine with placebo (1241 children randomized to atomoxetine and 756 randomized to placebo) and a total of 14 short-term trials compared methylphenidate with placebo (1100 children randomized to methylphenidate and 670 randomized to placebo). The effect sizes for symptom reduction and overall functioning showed a statistically significant advantage for methylphenidate (SMD -0.48, 95% CI -1.06 to -0.62) and atomoxetine (SMD -0.58, 95% CI -0.69 to -0.48) over placebo. The size of the effect was moderate for both medicines. The evidence for dexamphetamine is less robust (6 trials; 143 children randomized to dexamphetamine and 135 randomized to placebo, data not pooled). One study that directly compared methylphenidate with atomoxetine (166 patients randomized to methylphenidate and 164 to atomoxetine) failed to show significant differences in terms of symptoms, but showed a difference in terms of treatment acceptability (total dropouts) in favour of methylphenidate.
Summary of the quality of evidence	The quality of evidence for symptom reduction and functioning was MODERATE for both medicines (see GRADE tables for details).
Balance of benefits versus harms	The efficacy of methylphenidate and Atomoxetine should be balanced with adverse effects that may be particularly relevant in the long-term, including decreased appetite with associated weight loss and cardiovascular problems.

	Atomoxetine may have less potential for misuse compared with stimulants and does not require the same strict prescribing and storage conditions as methylphenidate. Methylphenidate has been used for over 50 years for the treatment of ADHD. The rate of sudden death with CNS stimulant has been estimated, per 100,000 patient-years, as 0.2 for methylphenidate and 0.5 for atomoxetine. The differences are not in excess of the baseline rate of sudden death in the paediatric population, which is estimated to be 1.3–1.85/100,000.
Values and preferences including any variability and human rights issues	Lack of functioning (school, family, social) associated with symptoms of ADHD (favours treatment); Stigma associated with symptoms of ADHD (favours treatment); Adverse effects and safety in the long-term (a proxy of this is the availability and use of a medicine for many years in other settings) (favours methylphenidate over atomoxetine); Risk of misuse and diversion (favours atomoxetine over methylphenidate); Stigma associated with receiving medicines to control a behavioural disorder (against treatment); Psychosocial interventions backed by scientific evidence should be provided before pharmacological interventions (against medicines as first-line treatment).
Costs and resource use and any other relevant feasibility issues	Training is required to properly recognize children with ADHD and to regularly monitor the risk of adverse effects and medicine misuse. Methylphenidate is associated with lower acquisition costs compared with atomoxetine in most settings; Methylphenidate is available in LAMIC compared to atomoxetine which has only recently been developed; Methylphenidate and atomoxetine are not in the 2007 Essential Medicines

	List for children (but both were under consideration in 2008).

Recommendation(s)

Non-specialized health care providers at the secondary level should consider initiating parent education/training before starting medication for a child who has been diagnosed as suffering from Attention-deficit hyperactivity disorder (ADHD). Initial interventions may include cognitive behaviour therapy and social skills training if feasible.

Strength of recommendation: STANDARD

Methylphenidate may be considered, when available, after a careful assessment of the child, preferably in consultation with relevant specialist and taking into consideration, the preferences of parents and children. Children receiving methylphenidate should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse effects. Care and support should be provided for the parents, if needed.

Strength of recommendation: STANDARD

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Ghanizadeh A. Atomoxtetine for Treating ADHD Symptoms in Autism: A Systematic Review. Journal of Attention Disorders 2012, DOI: 10.1177/1087054712443154

Keen D, Hadjikoumi I. ADHD in children ad adolescents, Clinical Evidence 2011;02:312 (Search date August 2009).

Montoya A, Colom F, Ferrin M. Is psychoeducation for parents and teachers of children and adolescents with ADHD efficacious? A systematic literature review

European Psychiatry, 2011; 26: 166 – 175.

Pringsheim T, Steeves T. Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD007990. DOI: 10.1002/14651858. CD007990.pub2.(**New, published in Issue 4, 2011**.)