Q8: What is the effectiveness, safety and role of pharmacological interventions, by non-specialized health care providers, for the broad category of Disruptive Behaviour Disorders (DBDs), Conduct Disorder (CD), Oppositional Defiant Disorder (ODD) and comorbid (but not exclusively) Attention-Deficit Hyperactivity Disorder (ADHD)?

Background

Children and adolescents are commonly referred to health care services because of their behavioural problems. Disruptive Behaviour Disorders (DBD) include Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorders (CD). ADHD seems to be the most commonly diagnosed among all such disorders affecting more boys than girls. However, the diagnosis of hyperkinetic disorder or ADHD remains a controversial issue surrounded with concerns about context as it may be symptomatic of family dysfunction, rather than individual psychopathology, and may reflect inadequacies in the educational system. Median medical costs for children with a diagnosis of ADHD is considerably higher as compared with those without this disorder, owing to higher rates of emergency health care and visits for outpatient care to primary care clinicians. Conduct disorders are common and tend to persist into adolescence and adult life through drug abuse, juvenile delinquency, adult crime, antisocial behaviour, marital problems, poor employee relations, unemployment, interpersonal problems, and poor physical health. Similar to ADHD, increased costs for care and to society in later years from the childhood diagnosis of conduct disorder has been demonstrated. ADHD is considered generally more treatable and stimulants have been used as the drug of choice. But it is not clear to what extent pharmacologic interventions can help and which tier of health care are qualified to offer this. There is even less evidence for the treatment of other disruptive disorders but even non-specialized heath care providers especially in low and middle income countries may be demanded to treat them by the parents, teachers or care givers.

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

Population: children with Disruptive Behaviour Disorders (DBD), Conduct Disorder (CD), Oppositional Defiant Disorder (ODD), and comorbid (but not exclusively) Attention-Deficit Hyperactivity Disorder (ADHD)

Interventions: carbamazepine

lithium

methylphenidate

risperidone

Pharmacological interventions for children with Disruptive Behaviour Disorders or Conduct Disorder or Oppositional Defiant Disorder

Comparator: placebo

Outcomes: aggression

family/School Functioning

human Rights

safety/tolerability issues

symptom reduction/clinical improvement

treatment satisfaction

user Satisfaction

List of the systematic reviews identified by the search process

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews
I	**Carbamazepine vs. Placebo**	Symptom reduction/clinical improvement (efficacy)	Ipser & Stein (2007)
		Aggression	
		Family/School Functioning	
		Safety/tolerability issues	
		Treatment satisfaction	
		Human Rights	
		User Satisfaction	
I	**Lithium vs. Placebo**	Symptom reduction/clinical improvement (efficacy)	Ipser & Stein (2007)

		Aggression	
		Family/School Functioning	
		Safety/tolerability issues	
		Treatment satisfaction	
		Human Rights	
		User Satisfaction	
I	**Methylphenidate vs. Placebo**	Symptom reduction/clinical improvement (efficacy)	Ipser & Stein (2007)
		Aggression	
		Family/School Functioning	
		Safety/tolerability issues	
		Treatment satisfaction	
		Human Rights	
		Treatment satisfaction	
		User Satisfaction	
I	**Risperidone vs. Placebo**	Symptom reduction/clinical improvement (efficacy)	Ipser & Stein (2007)
		Aggression	
		Family/School Functioning	
		Safety/tolerability issues	
		Treatment satisfaction	
		Human Rights	
		User Satisfaction	

Narrative description of the studies that went into the analysis

CARBAMAZEPINE VERSUS PLACEBO

According to Ipser & Stein (2007), only one trial with information suitable for re-analysis compared carbamazepine with placebo (12 children randomized to carbamazepine and 12 randomized to placebo).The study was double-blind, patient age ranged between 5-12 years and carbamazepine mean dose was 683 mg/day. Length of follow-up was 6 weeks.

Study by study table:

	DB	Setting	Follow-up	Carbamazepine/Placebo	Age range
Cueva 1996 (CD)	Yes		6 weeks	12/12 683mg/day	5-12

LITHIUM VERSUS PLACEBO

According to Ipser & Stein (2007), only two trials with information suitable for re-analysis compared lithium with placebo (45 children randomized to lithium and 45 randomized to placebo).The studies were double-blind, patient age ranged between 5-17 years and lithium mean dose was between 900 and 2,100 mg/day. Length of follow-up was 4 weeks in both studies.

Study by study table:

	DB	Setting	Follow-up	Lithium/Placebo	Age range
Campbell, 1995 (CD)	Yes		4 weeks	25/25 children 1,248mg/day	5-12
Malone et al, 2000 (CD)	Yes		4 weeks	20/20 children 900-2,100 mg/day	10-17

METHYLPHENIDATE VERSUS PLACEBO

According to Ipser & Stein (2007), only two trials with information suitable for re-analysis compared methylphenidate with placebo (50 children randomized to methylphenidate and 48 randomized to placebo).The studies were double-blind, patient age ranged between 6-17 years and methylphenidate mean dose was between 10 and 41.3 mg/day. Length of follow-up was 4-5 weeks.

Study by study table:

	DB	Setting	Follow-up	MTP/Plo	Age range
Klein et al,	Yes		5 weeks	37/37	6-15

1997 (DCD and ADHD)				41.3mg/day	
Spencer et al, 2006 (ODD and ADHD)	Yes		4 weeks	13/11 10-40mg/day	6-17

RISPERIDONE VERSUS PLACEBO

According to Ipser & Stein (2007), only two trials with information suitable for re-analysis compared risperidone with placebo (29 children randomized to risperidone and 29 randomized to placebo).The studies were double-blind, patient age ranged between 6-14 years and risperidone mean dose was between 0.75 and 1.5 mg/day. Length of follow-up was 6-10 weeks.

Study by study table:

	DB	Setting	Follow-up	RISP/Plo	Age range
Buitelaar et al, 2001 (DBD and ADHD)	Yes		6 weeks	19/19 2.9mg/day	6-14
Findling et al, 2000 (CD)	Yes		10 weeks	10/10 0.75-1.5mg/day	6-14

GRADE tables

Table 1

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-23
Question: Should carbamazepine vs. placebo be used for DBD?[1]
Settings:
Bibliography: Ipser J, Stein DJ (2007). Systematic review of pharmacotherapy of disruptive behaviour disorders in children and adolescents. *Psychopharmacology*, 191:127-40.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	carbamazepine	placebo	Relative (95% CI)	Absolute		
Clinical improvement												
1[2]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	very serious[4]	none	3/11 (27.3%)	3/11 (27.3%)	RR 1.0 (0.26 to 3.91)	0 fewer per 1000 (from 202 fewer to 794 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Aggression (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		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) (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		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 Ipser & Stein (2007), only one trial with information suitable for re-analysis compared carbamazepine with placebo (12 children randomized to carbamazepine and 12 randomized to placebo).The study was double-blind, patient age ranged between 5-12 years and carbamazepine mean dose was 683 mg/day. Length of follow-up was 6 weeks.

[2] Page 134 of Ipser & Stein (2007).

[3] Only one study contributed to this outcome so we have doubts about the applicability of study findings.

[4] Less than 50 patients were included, plus the 95% confidence interval includes no effect ranging from appreciable benefit to appreciable harm.

Table 2

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-23
Question: Should lithium vs. placebo be used for DBD?[1]
Settings:
Bibliography: Ipser J, Stein DJ (2007). Systematic review of pharmacotherapy of disruptive behaviour disorders in children and adolescents. *Psychopharmacology*, 191:127-40.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lithium	placebo	Relative (95% CI)	Absolute		
Clinical improvement												
2[2]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	24/45 (53.3%)	5/45 (11.1%)	RR 4.22 (1.83 to 9.74)	358 more per 1000 (from 92 more to 971 more)	⨁⨁⨁◯ LOW	IMPORTANT
Aggression (Better indicated by lower values)												
1[5]	randomized trials	no serious limitations	no serious inconsistency	serious[6]	very serious[7]	none	20	20	-	SMD 0.56 lower (1.19 lower to 0.07 higher)	⨁◯◯◯ VERY 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) (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		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 Ipser & Stein (2007), only two trials with information suitable for re-analysis compared lithium with placebo (45 children randomized to lithium and 45 randomized to placebo).The studies were double-blind, patient age ranged between 5-17 years and lithium mean dose was between 900 and 2,100 mg/day. Length of follow-up was 4 weeks in both studies.
[2] Page 134 of Ipser & Stein (2007).
[3] Less than 100 patients were included.
[4] Few participants, few trials.
[5] Page 135 of Ipser & Stein (2007).
[6] Only one study contributed to this outcome so we have doubts about the applicability of study findings.
[7] Less than 50 patients were included, plus the 95% confidence interval includes no effect ranging from appreciable benefit to no benefit.

Table 3

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-23
Question: Should methylphenidate vs. placebo be used for DBD?[1]
Settings:
Bibliography: Ipser J, Stein DJ (2007). Systematic review of pharmacotherapy of disruptive behaviour disorders in children and adolescents. *Psychopharmacology*, 191:127-40.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	methylphenidate	placebo	Relative (95% CI)	Absolute		
Clinical improvement												
1[2]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	very serious[4]	none	8/13 (61.5%)	4/11 (36.4%)	RR 1.69 (0.69 to 4.13)	251 more per 1000 (from 113 fewer to 1138 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Aggression (Better indicated by lower values)												
1[5]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	serious[6]	none	37	37	-	SMD 4.55 lower (5.43 to 3.67 lower)	⨁◯◯◯ 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) (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		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 Ipser & Stein (2007), only two trials with information suitable for re-analysis compared methylphenidate with placebo (50 children randomized to methylphenidate and 48 randomized to placebo).The studies were double-blind, patient age ranged between 6-17 years and methylphenidate mean dose was between 10 and 41.3 mg/day. Length of follow-up was 4-5 weeks.

[2] Page 134 of Ipser & Stein (2007).

[3] Only one study contributed to this outcome so we have doubts about applicability of study findings.

[4] Less than 50 patients were included, plus the 95% confidence interval includes no effect ranging from appreciable benefit to no benefit.

[5] Page 135 of Ipser & Stein (2007).

[6] Less than 100 patients were included.

Table 4

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-04-23
Question: Should risperidone vs. placebo be used for DBD?[1]
Settings:
Bibliography: Ipser J, Stein DJ (2007). Systematic review of pharmacotherapy of disruptive behaviour disorders in children and adolescents. *Psychopharmacology*, 191:127-40.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**risperidone**	**placebo**	**Relative (95% CI)**	**Absolute**		
Symptom reduction (Better indicated by lower values)												
2[2]	randomized trials	no serious limitations	very serious[3]	no serious indirectness	serious[4]	none	29	29	-	MD 2.19 lower (3.07 to 1.31 lower)	⨁⨁⨁◯ VERY LOW	IMPORTANT
Aggression (Better indicated by lower values)												

2[5]	randomized trials	no serious limitations	very serious[6]	no serious indirectness	very serious[4,7]	none	29	29	-	SMD 1.30 lower (3.56 lower to 0.96 higher)	⨁◯◯◯ VERY 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) (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		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 Ipser & Stein (2007), only two trials with information suitable for re-analysis compared risperidone with placebo (29 children randomized to risperidone and 29 randomized to placebo).The studies were double-blind, patient age ranged between 6-14 years and risperidone mean dose was between 0.75 and 1.5 mg/day. Length of follow-up was 6-10 weeks.

[2] Page 134 of Ipser & Stein (2007).

[3] Heterogeneity exceeds 75% (I-squared 77.3%).

[4] Less than 100 patients were included.

[5] Page 135 of Ipser & Stein (2007).

[6] Heterogeneity exceeds 75% (I-squared 90.6%).

[7] Less than 100 patients were included, plus the 95% confidence interval includes no effect ranging from appreciable benefit to appreciable harm.

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

CARBAMAZEPINE:

Safety table	Source document
Frequent adverse events: Increased levels of dizziness, increased appetite, transient leukopenia	Page 136 of Ipser & Stein (2007)

LITHIUM:

Safety table	Source document
Frequent adverse events: Nausea, vomiting	Page 136 of Ipser & Stein (2007)

METHYLPHENIDATE:

Safety table	Source document
Frequent adverse events: Decreased appetite, anorexia, insomnia, headache, abdominal pain. 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 136 of Ipser & Stein (2007) 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 behaviour (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	Page 10 of Keen & Hadijikoumi (2008) Page 10 of Keen & Hadijikoumi (2008)

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.	

RISPERIDONE:

Safety table	**Source document**
Frequent adverse events: Drowsiness, vomiting, weight gain, extrapyramidal symptoms, somnolence Increased appetite, weight gain and metabolic disturbances	 Page 136 of Ipser & Stein (2007) Page 290 0f NICE (2009)

References

Buitelaar JK et al (2001). A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. *Journal of Clinical Psychiatry,* 62:239–48.

Campbell M (1995). Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34:445–53.

Findling RL et al (2000). A double-blind pilot study of risperidone in the treatment of conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39:509–16.

Ipser J, Stein DJ (2007). Systematic review of pharmacotherapy of disruptive behaviour disorders in children and adolescents. *Psychopharmacology*, 191:127-40.

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

Klein RG et al (1997). Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Archives of General Psychiatry,* 54:1073–80.

Malone RP et al (2000). A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Archives of General Psychiatry,* 57:649–54.

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.

Spencer TJ et al (2006). Efficacy and safety of mixed amphetamine salts extended release (adderall XR) in the management of oppositional defiant disorder with or without comorbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-doseescalation study. *Clinical Therapeutics*, 28:402–18.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	One trial with information suitable for re-analysis compared carbamazepine with placebo. The effect size for clinical improvement showed no significant advantage for carbamazepine (RR 1.0 (0.26 to 3.91)). Two trials with information suitable for re-analysis compared lithium with placebo. A strong advantage was shown for lithium compared to placebo for clinical improvement (RR 4.22 (1.83 to 9.74)). Two trials with information suitable for re-analysis compared methylphenidate with placebo. The effect size for clinical improvement showed no significant advantage for methylphenidate versus placebo (RR 1.69 (0.69 to 4.13)), but there was a significant reduction in aggression (SMD 4.55 lower (5.43 to 3.67 lower)). Two trials with information suitable for re-analysis compared risperidone with placebo. The effect size for symptom reduction showed a significant improvement for risperidone compared to placebo (MD 2.19 lower (3.07 to 1.31) lower), but no significant improvement in aggression (SMD 1.30 lower (3.56 lower to 0.96 higher)).

Pharmacological interventions for children with Disruptive Behaviour Disorders or Conduct Disorder or Oppositional Defiant Disorder

Summary of the quality of evidence	The quality of evidence varied from LOW to VERY LOW.
Balance of benefits versus harms	The potential for harm is high in using all of the mentioned medicines, this ranges from side effects to possibility of severe complications such as renal insufficiency or leucopenia . While the possibility of achieving positive results is low or very low.
Values and preferences including any variability and human rights issues.	Preventing harm is the first principle in treatment. On the other hand the disruptive disorders mentioned above need treatment to protect the child or adolescent and the communities as well. Other less harmful and more effective treatments should be suggested for the above mentioned disorders.
Costs and resource use and any other relevant feasibility issues.	Alternative approaches to treatment such as psychosocial and family interventions require training for the health care staff. The amount of time spent in administering such treatment should also be realistic.
Recommendation(s) Pharmacological interventions (such as methylphenidate, lithium, carbamazepine and risperidone) should not be offered by non-specialized health care providers to treat Disruptive Behaviour Disorders (DBD), Conduct Disorder (CD), Oppositional Defiant Disorder (ODD) and comorbid Attention-deficit hyperactivity disorder (ADHD). For these conditions, the patients should be referred to specialist before prescribing any medicines. Strength of recommendation: STRONG	

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. No new systematic reviews were found to be relevant.