Q10: Are antidepressants (Tricyclic antidepressants (TCA), Selective serotonin reuptake inhibitors (SSRIs)) effective and safe in children 6-12 years of age with depressive episode/disorder?

Background

Compared with adult depression, depression in children (6–12 years) may have a more insidious onset, may be characterized more by irritability than sadness, and occurs more often in association with other conditions such as anxiety, conduct disorder, hyperkinesis, and learning problems. The prevalence of major depression is estimated to be approximately 2% in children.

In children with depression, pharmacological treatment is based on antidepressant drugs, initially tricyclic antidepressants and more recently selective serotonin reuptake inhibitors (SSRIs). Although the population to be covered in this scoping question includes children only, it is anticipated that some randomized controlled trials, and some meta-analyses included in systematic reviews, were carried out in the group of children and adolescents considered together. The body of evidence is therefore presented for children only whenever possible, and for children and adolescents considered together if no data are available for adolescents only.

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

Population:	children (6-12 years) with depressive episode/disorder
Interventions:	antidepressant drugs: Tricyclics and related, selective serotonin reuptake inhibitors
Comparator:	placebo
Outcomes:	symptom reduction
	overall performance at school

family functioning

adverse effects of treatment

improvement in physical health

user and family satisfaction

reduction in risk behaviour

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

Hazell P et al (2002). Tricyclic drugs for depression in children and adolescents. *Cochrane Database of Systematic Reviews*, (2):CD002317. Last assessed as up-to-date: 11 February 2008.

Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

EXCLUDED FROM GRADE TABLES

Hazell P (2009). Depression in children and adolescents. *BMJ Clinical Evidence*, 01:1008.

NICE (2005). Depression in Children and Young People. Identification and management in primary, community and secondary care. National Clinical Practice Guideline Number 28. London: The British Psychological Society & The Royal College of Psychiatrists.

Tsapakis EM et al (2008). Efficacy of antidepressants in juvenile depression: meta-analysis. *British Journal of Psychiatry,* 193:10-17.

Whittington CJ et al (2004). Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet,* 363:1341-5.

Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

Usala T et al (2008). Randomized controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis. *European Neuropsychopharmacology*, 18:62-73.

Dubicka B, Hadley S, Robertrs C (2006). Suicidal behaviour in youths with depression treated with new-generation antidepressants. Meta-analysis. *British Journal of Psychiatry*, 189:393-8.

Hammad TA, Laughren T, Racoosin J 2006). Suicidality in paediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*, 63:332-9.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	**Tricyclics and related vs. placebo**	Symptoms Overall performance at school Family functioning Adverse effects of treatment (acceptability profile) Improvement in physical health User and family satisfaction Reduction in risk behaviour	Hazell et al, 2002 (update 2008) No data No data No data No data No data No data	Hazell et al, 2002 (update 2008) is a recently updated Cochrane Review
3	**Individual SSRI vs. placebo**	Symptoms Overall performance at school	Hetrick et al (2007) No data No data	Hetrick et al (2007) is a recently published Cochrane Review

		Family functioning Adverse effects of treatment (acceptability profile) Improvement in physical health User and family satisfaction Reduction in risk behaviour	Hetrick et al (2007) No data No data	

Narrative description of the studies that went into the analysis

According to Hazell et al (2002) Cochrane Review on tricyclic antidepressants, thirteen studies reported data in a manner that could be extracted and pooled. Seven trials were directed to adolescents (aged 12 years and over), four trials were directed to children (aged 12 years and under) and two trials involved subjects spanning childhood and adolescence. Participants were outpatients in seven trials, inpatients of child or adolescent psychiatric units in five trials, and a mixture of inpatients and outpatients in one trial. Five trials involved imipramine, four trials involved amitriptyline, two trials involved desipramine and two trials involved nortriptyline. The control treatment in all cases was inactive placebo. Follow up intervals ranged from 4 weeks to 10 weeks. The shorter follow up intervals are arguably insufficient to adequately determine treatment responsiveness.

According to Hetrick Cochrane Review, of 12 trials comparing one of the SSRIs with placebo were eligible for inclusion, and 10 of these included data that could be extracted and pooled in one or more meta-analyses. There were three trials of paroxetine, four trials of fluoxetine, two trials of citalopram, one of escitalopram and two trials of sertraline. There were five trials in adolescents with an age range of 12 or 13 to 17 or 18, and seven in children and adolescents with a lower age limit of between 6-8 years. The treatment period of the included trials was between 7 and 12 weeks. All trials were of major depressive disorder and all except one stated that diagnoses were based on a structured clinical interview such as the K-SADS-P & L. Authors of all reports, except one describe depressive disorder symptom severity at baseline for the treatment and placebo groups. Mean severity scores at baseline from the individual trials range from 54.5 to 65.5 on the CDRS-R (range 17 - 113) and from 25.9 to 32.5 on the K-SADS 9 item depression score (range 9 - 56).

GRADE tables

Table 1

[Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder]

Author(s): Corrado Barbui, Taghi Yasamy

Date: 2009-05-25

Question: Should tricyclic antidepressants vs. placebo be used for children with depression?

Settings:

Bibliography: Hazell P et al (2002). Tricyclic drugs for depression in children and adolescents. *Cochrane Database of Systematic Reviews*, (2):CD002317. Last assessed as up-to-date: 11 February 2008.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tricyclic antidepressants	placebo	Relative (95% CI)	Absolute		
lack of response												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	25/39 (64.1%)	27/38 (71.1%)	OR 0.69 (0.25 to 1.89)	82 fewer per 1000 (from 330 fewer to 112 more)	⨁◯◯◯ VERY LOW	CRITICAL
depressive symptoms (Better indicated by lower values)												
3[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	34	31	-	SMD 0.15 higher (0.34 lower to 0.64 higher)	⨁◯◯◯ LOW	CRITICAL
overall functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects												
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 and family satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.4 of Hazell et al (2002) Cochrane Review.
[2] Unclear dropout in one study, unclear randomization and allocation concealment.
[3] Less than 100 patients are included in the analysis, and the estimate ranges from appreciable benefit to appreciable harm.
[4] From Analysis 1.6 of Hazell Cochrane Review.
[5] Unclear dropouts in two studies, unclear randomization and allocation concealment.

Table 2

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-05-25
Question: Should citalopram vs. placebo be used for children with depression?
Settings:
Bibliography: Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	citalopram	placebo	Relative (95% CI)	Absolute		
Response												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
depressive symptoms (Better indicated by lower values)												
1[1]	randomized trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	0[5]	0[5]	-	MD 0.05 lower (6.02 lower to 5.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL
overall functioning (Better indicated by lower values)												
1[6]	randomized trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	0[5]	0[5]	-	MD 1.8 lower (6.89 lower to 3.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL

adverse effects												
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 and family satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 5.2 of Hetrick et al (2007) Cochrane Review.
[2] Dropout rate exceeds 30%.
[3] Only one study contributed to the analysis.
[4] Estimate ranges from appreciable benefit to appreciable harm.
[5] Not reported.
[6] From Analysis 5.2 of Hetrick et al (2007) Cochrane Review.

Table 3

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-05-25
Question: Should fluoxetine vs. placebo be used for children with depression?
Settings:
Bibliography: Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	fluoxetine	placebo	Relative (95% CI)	Absolute		
Response												
1[1]	randomized trials	no serious limitations	no serious inconsistency	very serious[2]	serious[3]	None	27/61 (44.3%)	10/55 (18.2%)	RR 2.43 (1.3 to 4.56)	260 more per 1000 (from 55 more to 647 more)	⨁⨁◯◯ VERY LOW	CRITICAL

depressive symptoms (Better indicated by lower values)												
2[4]	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	None	0[6]	0[6]	-	MD 6.72 lower (10.55 to 2.88 lower)	⨁⨁⨁◯ LOW	CRITICAL
overall functioning (Better indicated by lower values)												
1[7]	randomized trials	very serious[8]	no serious inconsistency	serious[2]	serious[9]	None	0[6]	0[6]	-	MD 3.76 higher (3.19 lower to 10.71 higher)	⨁◯◯◯ VERY LOW	CRITICAL
adverse effects												
0	no evidence available					None	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
user and family satisfaction (Better indicated by lower values)												
0	no evidence available					None	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 3.1 of Hetrick et al (2007) Cochrane Review.
[2] Only one study contributed to the analysis.
[3] Less than 100 patients are included in the analysis.
[4] From Analysis 3.2 of Hetrick et al (2007) Cochrane Review.
[5] One study has a dropout rate exceeding 30%.
[6] Not reported.
[7] From Analysis 3.3 of Hetrick et al (2007) Cochrane Review.
[8] Dropout rate exceeds 30%.
[9] Estimate ranges from appreciable benefit to appreciable harm.

Table 4

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-05-25
Question: Should paroxetine vs. placebo be used for children with depression?
Settings:
Bibliography: Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	paroxetine	placebo	Relative (95% CI)	Absolute		
Response												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[3]	none	22/49 (44.9%)	22/47 (46.8%)	RR 0.96 (0.62 to 1.48)	19 fewer per 1000 (from 178 fewer to 225 more)	⨁⨁◯◯ LOW	CRITICAL
depressive symptoms (Better indicated by lower values)												
1[4]	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[5]	none	0[6]	0[6]	-	MD 5.27 higher (0.00 to 10.54 higher)	⨁⨁◯◯ LOW	CRITICAL
overall functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects												
1	randomized trials[7]	no serious limitations	no serious inconsistency	serious[2]	serious[3]	none	34/49 (69.4%)	30/47 (63.8%)	RR 1.09 (0.82 to 1.44)	57 more per 1000 (from 115 fewer to 281 more)	⨁⨁◯◯ LOW	CRITICAL
user and family satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.1 of Hetrick et al (2007) Cochrane Review.
[2] Only one study contributed to the analysis.
[3] Estimate ranges from appreciable benefit to appreciable harm.
[4] From Analysis 1.2 of Hetrick et al (2007) Cochrane Review.
[5] Estimate rangesa from appreciable harm to no difference.
[6] Not reported.
[7] From Analysis 1.8 of Hetrick et al (2007) Cochrane Review.

Table 5

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-05-25
Question: Should sertraline vs. placebo be used for children with depression?
Settings:
Bibliography: Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	sertraline	placebo	Relative (95% CI)	Absolute		
Response												
0	no evidence available					None	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
depressive symptoms (Better indicated by lower values)												
2[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[3]	None	0[4]	0[4]	-	MD 2.34 lower (7.01 lower to 2.33 higher)	⨁⨁⨁◯ LOW	CRITICAL
overall functioning (Better indicated by lower values)												
0	no evidence available					None	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects												
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 and family satisfaction (Better indicated by lower values)												
0	no evidence available					None	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 4.2 of Hetrick et al (2007) Cochrane Review.
[2] Both included studies are from the same research group so directness may be a problem.
[3] Estimate ranges from appreciable benefit to appreciable harm.
[4] Not reported.

Table 6

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-06-16
Question: Should selective serotonin reuptake inhibitors vs. placebo be used for children with depression?
Settings:
Bibliography: Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	selective serotonin reuptake inhibitors	placebo	Relative (95% CI)	Absolute		
Suicide ideas / behaviour (children and adolescents, 6-18 years)												
9[1]	randomized trials	very serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	57/978 (5.8%)	30/886 (3.4%)	RR 1.73 (1.13 to 2.67)	25 more per 1000 (from 4 more to 57 more)	⨁⨁⨁◯ VERY LOW	CRITICAL

[1] From Analysis 6.2 of Hetrick et al (2007) Cochrane Review.
[2] Four studies reported a dropout rate higher than 30%.
[3] Children and adolescents are considered together.

Additional information that was not GRADEd (safety and tolerability issues, cost, resource use, and other feasibility issues, if appropriate)

From NICE (2005):

Tricyclic antidepressants

In children and young people, it is unlikely that tricyclic antidepressants have clinically important benefits over placebo for remission, response to treatment (50% reduction in symptoms) or reduction in symptoms. At least in young people, there is limited evidence that Tricyclics produce more side effects than

placebo and are more likely to lead to discontinuation of treatment. It is also known that tricyclic antidepressants (except lofepramine) are highly toxic in overdose.

Fluoxetine (SSRI)

Fluoxetine (up to 40 mg/day for 7 to 12 weeks) showed efficacy across a range of outcomes in 7–18-year-olds. When compared with placebo, fluoxetine produced clinically important improvement in depressive symptoms (when measured with a clinician completed rating scale) and improved the likelihood of both remission and response to treatment, and had a positive impact regarding general clinical improvement and the severity of depression. Evidence is inconclusive regarding the impact on functional status. The relative risk of serious adverse events and suicidal behaviour is difficult to interpret because of wide confidence intervals, although the rate of harm-related adverse events and suicidal behaviour/ideation was higher in fluoxetine than placebo-treated patients. However, there is evidence that fluoxetine is less likely than placebo to lead to discontinuation of treatment for any reason. Treatment-emergent adverse events were generally similar between fluoxetine and placebo with the exception of hyperkinesias, headache and skin rash, where there is evidence suggesting increased risk for fluoxetine.

Paroxetine (SSRI)

In one study, paroxetine (up to 40 mg/day for 8 to 12 weeks) improved the likelihood of remission in 12–18-year-olds. However, further evidence suggested paroxetine had little impact on response to treatment, symptom levels, functional status, or clinical improvement. There is evidence suggesting that paroxetine is more likely than placebo to bring about serious adverse effects, and limited evidence of increased risk of suicidal behaviour/ideation and early discontinuation from treatment because of adverse events or any reason. Paroxetine is more likely than placebo to cause the following treatment-emergent adverse events: dizziness, hostility, insomnia, somnolence and tremor.

Sertraline (SSRI)

Sertraline (up to 200 mg/day for 10 weeks) when compared with placebo produced a small improvement in depressive symptoms in 6–17-year-olds. However, the evidence regarding remission, response to treatment, and clinical improvement is inconclusive. Evidence suggests no impact on functional status. There is evidence suggesting that children (6–11 years) treated with sertraline are more likely to discontinue treatment because of adverse events, and for children/young people there is limited evidence of increased risk of suicidal behaviour/ ideation. Evidence is inconclusive regarding serious adverse events. There is limited evidence for an increased risk of discontinuation of treatment for any reason. In children (6–11 years), sertraline is more likely than placebo to cause the following treatment-emergent adverse events: nausea, diarrhoea, and anorexia; and may increase the risk of vomiting, agitation, urinary incontinence, and purpura. In young people (12–17 years), sertraline is more likely than placebo to cause vomiting and diarrhoea.

Citalopram (SSRI)

Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

There was limited evidence that citalopram (up to 40 mg/day for 8 to 12 weeks), when compared with placebo, improved the chance of remission and response to treatment, and improved depressive symptoms in 7–18-year-olds. There was limited evidence that citalopram increases the risk of treatment-emergent adverse events, suicidal behaviour/ideation, early discontinuation because of suicide attempts, and early discontinuation because of adverse events. Citalopram is more likely than placebo to cause the following treatment-emergent adverse events: rhinitis, nausea, flu-like symptoms, fatigue, diarrhoea, and pharyngitis.

NICE (2005) conclusion:

Fluoxetine is the only SSRI/atypical antidepressant where there is evidence of clinical effectiveness across a range of outcome measures. The evidence suggests that tricyclic antidepressants should not be used. There is limited evidence that all SSRIs/atypical antidepressants (including fluoxetine) may increase the risk of suicidal ideation and/or behaviour and increase the risk of discontinuation of treatment because of adverse events.

In the WHO Model List of Essential Medicines for Children (WHO 2007) fluoxetine is included for the pharmacological treatment of adolescents (>8 years)

References

Dubicka B, Hadley S, Robertrs C (2006). Suicidal behaviour in youths with depression treated with new-generation antidepressants. Meta-analysis. *British Journal of Psychiatry*, 189:393-8.

Hammad TA, Laughren T, Racoosin J 2006). Suicidality in paediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*, 63:332-9.

Hazell P (2009). Depression in children and adolescents. *BMJ Clinical Evidence*, 01:1008.

Hazell P et al (2002). Tricyclic drugs for depression in children and adolescents. *Cochrane Database of Systematic Reviews*, (2):CD002317.

Hetrick SE et al (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, (3):CD004851.

NICE (2005). Depression in Children and Young People. Identification and management in primary, community and secondary care. National Clinical Practice Guideline Number 28. The British Psychological Society & The Royal College of Psychiatrists.

Tsapakis EM et al (2008). Efficacy of antidepressants in juvenile depression: meta-analysis. *British Journal of Psychiatry,* 193:10-17.

Usala T et al (2008). Randomized controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis. *European Neuropsychopharmacology*, 18:62-73.

Whittington CJ et al (2004). Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet,* 363:1341-5.

WHO (2007). WHO Model List of Essential Medicines for Children. Geneva, World Health Organization.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	In terms of proportion of children showing an improvement in depressive symptoms, the evidence for tricyclic antidepressants (TCAs) versus placebo is inconclusive and so it is not possible to determine if there is a clinically important difference (RR 0.86, 0.25 to 1.89). Similarly, in terms of score on a depression measure the evidence for tricyclic antidepressants (TCAs) versus placebo is inconclusive (SMD 0.15, -0.34 to 0.64). For most SSRIs, the evidence is sparse and so it is not possible to determine if there is a clinically important difference between individual SSRIs and placebo. For fluoxetine, in terms of responders and in terms of score on a depression measure, there is limited evidence suggesting a significant beneficial effect. In terms of treatment acceptability and adverse effects, the evidence is sparse and inconclusive. In terms of suicide ideas/behaviour, for the group of selective serotonin reuptake inhibitors, including children and adolescents together, there is

	evidence of a significant increased risk (RR 1.73, 1.13 to 2.67, absolute risk difference 2.5%). For the other critical outcomes, no evidence is available.
Summary of the quality of evidence	The quality of the evidence was LOW or VERY LOW
Balance of benefits versus harms	In studies carried out in children with acute-phase depressive episode, antidepressants are not associated with a clinically relevant beneficial effect. Among the group of the selective serotonin reuptake inhibitors, fluoxetine appears as the only drug with at least some initial evidence of a possibly positive balance of benefit versus harm. There are safety and tolerability concerns associated with antidepressant exposure in children, including the increased risk of suicide ideas and behaviour.
Values and preferences including any variability and human rights issues	In situations where children are exposed to severe ongoing social stressors, depressive disorder may be difficult to differentiate from a transient reaction, with a risk of medicalization of a social problem. A widely held value is that children – still in development – should only be exposed to drugs if other effective treatment options have been tried, if the condition is sufficiently severe and treatment is likely to lead to a substantial improvement and if information about long-term consequences is available.
Costs and resource use and any other relevant feasibility issues	Any cultural variations in depression that may exist will further increase the possibility for incorrect diagnosis and treatment by people trained in a standard package. In many LAMIC, continuous availability of psychotropic in non-specialized health care is a challenge Both tricyclic antidepressants and many selective serotonin reuptake inhibitors

	are associated with low acquisition costs. Fluoxetine is included in the WHO list of essential medicines for the treatment of depressive disorders in adolescents only (> 8 years).
Recommendation(s) Antidepressants (Tricyclic antidepressants (TCA), Selective serotonin reuptake inhibitors (SSRI)) should not be used for the treatment of children 6-12 years of age with depressive episode/disorder in non-specialist settings. Strength of recommendation: STRONG	

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:

Hazell P, O'Connell D, Heathcote D, Henry DA. Tricyclic drugs for depression in children and adolescents. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD002317. DOI: 10.1002/14651858.CD002317. (**Edited (no change to conclusions), published in Issue 4, 2010.)**

Hazell, P. Depression in children and adolescents. Clinical Evidence 2011;10:1008