Q 12: In children and adolescents with anxiety disorders, what is the effectiveness and safety, considering system issues in low- and middle-income countries, of using pharmacological interventions in non-specialist settings?

Background

Anxiety disorders in children and adolescents consist of a heterogeneous category of disorders. Interventions are many with varying results. At the extreme phobias and panic disorder can lead to significant social isolation and lack of educational and occupational attainment. When school refusal is included in this diagnostic grouping then the consequences can be seen as having multi-sectoral implications for both diagnosis and treatment. Children with anxiety symptoms commonly present with somatic presentations and non- specialized health care providers should be aware on how to mange them. It is not only important to know about the efficacy of treatments but also about potential harms to children and adolescents who present to primary and secondary care.

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

Population:	children with anxiety disorders
Interventions:	pharmacological interventions
Comparator:	placebo
Outcomes:	symptom reduction
	overall performance at school
	family functioning
	adverse effects

improvement in physical health

user and family satisfaction

reduction in risk behaviour

List of the systematic reviews identified by the search process

Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Fluoxetine vs. placebo	School functioning, family functioning, adverse effects, user and family satisfaction, physical health, symptom severity, reduction in risk behaviour.	Ipser et al (2009)	This was the most recent and comprehensive review identified.
2	Fluvoxamine vs. placebo	School functioning, family functioning, adverse effects, user and family satisfaction, physical health, symptom severity, reduction in risk behaviour.	Ipser et al (2009)	This was the most recent and comprehensive review identified.
3	Paroxetine vs. placebo	School functioning, family functioning, adverse effects, user and family satisfaction, physical health, symptom severity, reduction in risk behaviour.	Ipser et al (2009)	This was the most recent and comprehensive review identified.
4	Sertraline vs. placebo	School functioning, family functioning, adverse effects, user and family satisfaction, physical	Ipser et al (2009)	This was the most recent and comprehensive review identified.

		health, symptom severity, reduction in risk behaviour.		
5	Clomipramine vs. placebo	School functioning, family functioning, adverse effects, user and family satisfaction, physical health, symptom severity, reduction in risk behaviour.	Ipser et al (2009)	This was the most recent and comprehensive review identified.
6	Venlafaxine	School functioning, family functioning, adverse effects, user and family satisfaction, physical health, symptom severity, reduction in risk behaviour.	Ipser et al (2009)	This was the most recent and comprehensive review identified.

Narrative description of the studies that went into the analysis

The review by Ipser et al (2009) included 22 short term (<= 16 weeks) randomized controlled trials with a total of 2519 participants (average age 12 years). The 16 trials included in this analysis evaluated the efficacy of pharmacotherapy in treating GAD, SP, OCD, overanxious and avoidant disorders and selective mutism. The medication tested were mostly SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) and SNRIs (clomipramine and venlafaxine).

The review included two studies that report outcomes separately for children and adolescents (Wagner et al, 2004 and Rynn et al, 2007) that found little difference in treatment response between the age groups. Two other studies (Geller et al, 2004 and Riddle et al, 2001) reported a higher response rate in children than adolescents for short term treatment of OCD only. This is not of importance to us here as we are interested in all anxiety disorders and OCD is not of much concern in non-specialised health care settings (which is the focus of this question).

GRADE tables

Table 1

Author(s): Mears
Date: 2009-08-28
Question: Should fluoxetine vs. placebo be used for anxiety disorders?
Settings: children and adolescents in LAMIC
Bibliography: Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	fluoxetine	placebo	Relative (95% CI)	Absolute		
Overall performance at school - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Family functioning - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects of treatment (Risk ratio)												
3[1]	randomized trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision[4]	none	12/149 (8.1%)	3/156 (1.9%) 0%	RR 3.42 (1.14 to 10.25)	47 more per 1000 (from 3 more to 178 more) 0 more per 1000 (from 0 more to 0 more)	⍰⍰⍰ LOW	CRITICAL
Improvement in physical health, growth and development - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
User and family satisfaction - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT

Reduction in risk behaviour - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Symptom severity (Better indicated by lower values)												
3[5]	randomized trials	very serious[6]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	128	91	-	MD 0.5 lower (0.78 to 0.23 lower)	⨁⨁⨁◯ LOW	CRITICAL

[1] Birmaher et al (2003); Geller et al (2004); Riddle et al (1992).

[2] Two of the criteria were not met in 1 out of 3 of the trials (33%). Geller (2001a) had a drop out rate of 33% (31% fluoxetine, 37.5% placebo) and it was not clear whether the study was masked.

[3] I-squared = 0.0%.

[4] The overall number of individuals in the study was >200 (N=305) and the confidence interval did not include no effect (confidence interval does not include 1).

[5] Birmaher et al (2003); Geller et al (2001a); Liebowitz et al (2002).

[6] Two of the criteria were not met in 1 out of 3 of the trials (33%). Geller et al (2001a) had a drop out rate of 33% (31% fluoxetine, 37.5% placebo) and it was not clear whether the study was masked.

[7] I-squared = 0.0%.

Table 2

Author(s): Mears
Date: 2009-09-01
Question: Should fluvoxamine vs. placebo be used for anxiety disorders?
Settings: children and adolescents in LAMIC
Bibliography: Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

Quality assessment							**Summary of findings**					**Importance**
							No of patients		**Effect**		**Quality**	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**fluvoxamine**	**placebo**	**Relative (95% CI)**	**Absolute**		
Overall performance at school - not measured												

0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Family functioning - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects (Risk ratio)												
2	randomized trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/120 (6.7%)	1/128 (0.8%) 0%	RR 5.27 (0.9 to 30.76)	33 more per 1000 (from 1 fewer to 233 more) 0 more per 1000 (from 0 fewer to 0 more)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement in physical health - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
User and family satisfaction - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Reduction in risky behaviour - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Symptom severity (Better indicated by lower values)												
2	randomized trials[4]	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	118	126	-	MD 0.71 lower (1.49 lower to 0.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL

[1] Riddle et al (2001); RUPPASG 2001.

[2] 100% of studies unclear about randomization and 50% of studies (RUPPASG 2001) unclear about blinding.

[3] The confidence interval includes no effect (crosses 1) and appreciable harm (crosses 2.0).

[4] Riddle et al (2001); RUPPASG 2001.

[5] 100% of studies unclear about randomization and 50% of studies (RUPPASG 2001) unclear about blinding.

[6] The confidence interval includes no effect (crosses 0) and appreciable benefit/harm (crosses an effect size of 0.5 in both directions).

Table 3

Author(s): Mears
Date: 2009-09-01
Question: Should paroxetine be used for ?
Settings: children and adolescents LAMIC
Bibliography: Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	paroxetine	control	Relative (95% CI)	Absolute		
Overall performance in school - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Family functioning - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects (Risk ratio)												
1[1]	randomized trials	no serious limitations	no serious inconsistency[2]	no serious indirectness	serious[3]	none	9/165 (5.5%)	2/157 (1.3%) 0%	RR 4.28 (0.94 to 19.51)	42 more per 1000 (from 1 fewer to 236 more) 0 more per 1000 (from 0 fewer to 0 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Improvement in physical health - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
User and family satisfaction - not measured												

0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Reduction in risky behaviour - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Symptom severity - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL

[1] Wagner et al (2004).

[2] Not applicable as single study.

[3] The 95% confidence interval includes no effect (crosses 1) and appreciable benefit/harm (crosses a risk of 2).

Table 4

Author(s): Mears
Date: 2009-09-01
Question: Should sertraline vs. placebo be used for anxiety disorders?
Settings: children and adolescents LAMIC
Bibliography: Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

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**		
Overall performance in school - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Family functioning - not measured												

0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects (Risk ratio)												
3[1]	randomized trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	21/253 (8.3%)	6/199 (3%) 0%	RR 2.6 (1.1 to 6.15)	48 more per 1000 (from 3 more to 155 more) 0 more per 1000 (from 0 more to 0 more)	⨁⨁⨁◯ LOW	CRITICAL
Improvement in physical health - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
User and family satisfaction - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Reduction in risky behaviour - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Symptom severity (Better indicated by lower values)												
3	randomized trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	172	115	-	MD 0.8 lower (1.39 to 0.21 lower)	⨁⨁⨁◯ LOW	CRITICAL

[1] March et al (1998); POTS 2004, Walkup 2008.

[2] No explanation was provided.

[3] I-squared = 0.0%.

[4] One criterion not met in >30% (unclear blinding in March 1998).

Table 5

Author(s): Mears
Date: 2009-09-01
Question: Should clomipramine vs. placebo be used for anxiety disorders?
Settings: children and adolescents LAMIC
Bibliography: Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	clomipramine	placebo	Relative (95% CI)	Absolute		
Overall performance in school - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Family functioning - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects (Risk ratio)												
1	randomized trials[1]	very serious[2]	no serious inconsistency[3]	no serious indirectness	very serious[4]	none	1/31 (3.2%)	0/29 (0%) 0%	RR 2.81 (0.12 to 66.4)	0 more per 1000 (from 0 fewer to 0 more) 0 more per 1000 (from 0 fewer to 0 more)	⨁⨁⨁◯ VERY LOW	CRITICAL
Improvement in physical health - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
User and family satisfaction - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT

Reduction in risky behaviour - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Symptom severity (Better indicated by lower values)												
1[5]	randomized trials	very serious[6]	no serious inconsistency	serious[7]	no serious imprecision	none	31	29	-	MD 1.15 lower (1.70 to 0.60 lower)	⨁◯◯◯ VERY LOW	CRITICAL

[1] DeVeaugh-Geiss et al (1992).

[2] More than one criterion not met on 100% of studies (one study, DeVaugh-Geiss et al (1992), had unclear randomization and blinding).

[3] not applicable; just one study.

[4] Sample size <100 (N=60) and confidence interval includes no effect (crosses 1) and appreciable benefit/harm (crosses 2).

[5] DeVeaugh-Geiss et al (1992).

[6] More than one criterion not met on 100% of studies (one study, DeVaugh-Geiss et al (1992), had unclear randomization and blinding).

[7] Sample size <100 (N=60). No appreciable benefit or harm and confidence interval does not include 0 so only downgraded by one point.

Table 6

Author(s): Mears
Date: 2009-09-01
Question: Should venlafaxine vs. placebo be used for anxiety disorders?
Settings: children and adolescents LAMIC
Bibliography: Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	venlafaxine	placebo	Relative (95% CI)	Absolute		
Overall performance in school - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

Family functioning - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects (Risk ratio)												
2[1]	randomized trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	14/307 (4.6%)	17/303 (5.6%) 0%	RR 0.82 (0.41 to 1.63)	10 fewer per 1000 (from 33 fewer to 35 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement in physical health - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
User and family satisfaction - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Reduction in risky behaviour - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT
Symptom severity - not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

[1] March et al (2007); Rynn et al (2007).

[2] More than one criteria not met in >30% March et al (2007) had a dropout rate of >30% and Rynn et al (2007) had unclear methods of blinding and randomization).

[3] I-squared =0.0%.

[4] 95% confidence intervals include no effect (cross 1) and appreciable benefit/harm (cross a risk of 0.5).

Additional evidence that was not GRADEd

Effective non-pharmacological interventions for children and adolescents with anxiety disorders have been reported in the literature. There is support for the efficacy of psychosocial interventions and for involving parents in the treatment of children or adolescents with anxiety disorders (Silverman and Berman, 2001). The most thoroughly documented intervention is cognitive behavioural therapy (CBT), shown to be effective in treating anxiety disorders in children and adolescents compared to waiting list or attention controls (James et al, 2009).

References

Birmaher B et al (2003). Fluoxetine for the treatment of childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry,* 42:415–24.

DeVeaugh-Geiss J et al (1992). Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder - a multicenter trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 31:45–9.

Geller DA et al (2001a). Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: A placebo-controlled clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 40:773–9.

Geller DA et al (2004). Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: A randomized, multicenter, double-blind, placebocontrolled trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 43:1387–96.

Ipser JC et al (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Systematic Reviews,* (3):CD005170.

James ACJ, Soler A, Weatherall RW (2009). Cognitive behavioral therapy for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews, Issue 3.

Liebowitz MR et al (2002). Fluoxetine in children and adolescents with OCD: A placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 41:1431–8.

March JS et al (1998). Sertraline in children and adolescents with obsessive-compulsive disorder: A multicenter randomized controlled trial. *Journal of the American Medical Association,* 280:1752–6.

March JS et al (2007). A randomized controlled trial of venlafaxine ER versus placebo in paediatric social anxiety disorder. *Biological Psychiatry,* 62:1149–54.

Riddle MA et al (1992). Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry,* 31:1062–9.

Riddle MA et al (2001). Fluvoxamine for children and adolescents with obsessive-compulsive disorder: A randomized, controlled, multicenter trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 40:222–9.

Rynn MA et al (2007). Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: Two placebo-controlled trials. *The American Journal of Psychiatry,* 164:290–300.

Silverman WK and Berman SL (2001). Psychosocial interventions for anxiety disorders in children and adolescents: status and future directions. In Silverman WK and Treffers PDA. Anxiety disorders in children and adolescents. Research, assessments and intervention. Cambridge University Press.

The Paediatric OCD Treatment Study (POTS) team (2004). Cognitivebehavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder. *Journal of the American Medical Association,* 292:1969–76.

The Research Unit on Paediatric Psychopharmacology Anxiety Study Group (RUPPASG) (2001). Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *New England Journal of Medicine,* 344:1279–85.

Wagner KD et al (2004). A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Archives of General Psychiatry,* 61:1153–62.

Walkup JT et al (2008). Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *New England Journal of Medicine,* 359:2753–2766.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	There is only evidence for the effects of four drugs on symptom severity. All four drugs (fluoxetine, fluvoxamine, sertraline and clomipramine) reported a reduction in symptom severity compared to placebos. The greatest reported mean difference between intervention and placebo was for clomipramine (MD 1.15, 95% CI 0.6 to 1.7). However, this was for patients with OCD only and the quality of evidence was VERY LOW. Five of the six interventions reported a risk ratio >1 for adverse events compared to placebo.
Summary of the quality of evidence	For symptom severity and adverse effects, both critical outcomes, the quality of the evidence was VERY LOW and LOW, with just one profile being MODERATE (which applied to adverse effects of paroxetine). There was no evidence for the remaining outcomes.
Balance of benefits versus harms	All the pharmacological interventions, apart from venlafaxine, reported adverse events compared to placebos and for venlafaxine evidence quality was very low. The average dropout rate for the studies included was approximately 22% reflecting quite high drug-related adverse events. The benefit of a reduction in symptom severity needs to outweigh these harms. However, the strength of evidence for the effectiveness of pharmacological interventions is weak, whilst the strength of evidence for adverse events is stronger.
Values and preferences including any variability and human rights issues	Non-maleficence is presented as a key concept within ethical frameworks. The fact that the adverse effects of pharmacological interventions do not seem to be outweighed by the benefits of treatment provides an argument against the use of drugs in children and adolescents. This is especially important in children and adolescents who may have less

	autonomy in decision-making. A holistic approach to child and adolescent mental health, involving the family, is preferred.
Costs and resource use and any other relevant feasibility issues	The cost of these drugs is high with the exception of fluoxetine which is also on the WHO Essential Medicines List. The intervention must be appropriate for the non-specialized health care setting, rather than the specialized health care setting. There must be available human resources to prescribe safely and monitor any adverse effects of the drugs. Health workers should also be trained to identify OCD and refer to tertiary care.
Recommendation(s) Pharmacological interventions should not be considered in children and adolescents with anxiety disorders in non-specialist settings. 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:

Ipser JC, Stein DJ, Hawkridge S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD005170. DOI: 10.1002/14651858.CD005170.pub2. (**Edited (no change to conclusions), published in Issue 6, 2010**.)