[2015]

CH 4: Antidepressants among adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective. [2015]

SCOPING QUESTION: Are antidepressants (specifically, tricyclic antidepressants and selective serotonin reuptake inhibitors) effective and safe in adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective?

BACKGROUND

A recent review has proposed antidepressant medication treatment as an option in adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective (Hetrick et al., 2012). The most commonly prescribed antidepressant medication in adolescents with moderate-severe depressive disorder were initially tricyclic antidepressants (TCAs) and, more recently, selective serotonin reuptake inhibitors (SSRIs) (Qiu et al., 2014).

In 2009, WHO recommended that fluoxetine, but not TCAs or other SSRIs, may be considered as one possible treatment in non-specialist settings of adolescents with depressive episodes. It was also recommended that adolescents on fluoxetine should be monitored closely for suicidal ideas and/or behaviours and that treatment support and supervision from a mental health specialist should be obtained, if available.

Although the population covered in this evidence profile includes adolescents only, it is anticipated that some randomized controlled trials, as well as some meta-analyses included in systematic reviews, were carried out in groups of children and adolescents considered together. Therefore, the body of evidence is presented for adolescents only whenever possible and for children and adolescents together if no data are available for adolescents only.

For the purpose of this review, the term *adolescents* refers to individuals who are 12–19 years old.

This evidence profile seeks to update the available evidence related to the scoping question and, if indicated, the current recommendation. In terms of antidepressant medication classes, the evidence is presented for TCAs and SSRIs groups. Additionally, the evidence is also presented for each individual SSRI. TCAs were not considered separately for this review because the effects of different TCAs are similar.

[2015]

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective
- **Interventions:** SSRIs and TCAs
- **Comparison:** Placebo
- **Outcomes:**
  - **Critical outcomes**: Reduction of symptoms, improved functioning/quality of life, adverse effects (i.e., suicidality)
  - **Important outcome**: Remission, adverse effects (i.e., number of withdrawals (dropouts))

Search strategy

In order to locate relevant systematic reviews, the following databases were searched: MEDLINE, Embase, the Cochrane Library, BMJ Clinical Evidence and PsychINFO, as well as regional databases comprising evidence from low- and middle-income countries (e.g., LAMICs) up to July 2014. Search strategies developed by McMaster University were adapted to locate relevant systematic reviews. For example, the following search was developed for use on Medline:

- #1 Add Search (meta analysis[Publication Type] or meta analysis [Title/Abstract] or meta analysis [MeSH Terms] or review [Publication Type] or search*[Title/Abstract]
- #2 Add Search (depression or depressive disorders or major depression or unipolar major depression)
- #3 Add Search (children or adolescent)
- #4 Add Search (antidepressant or selective serotonin reuptake inhibitors or tricyclic or new generation antidepressant)
- #5 Add Search (#1 and #2 and #3 and #4)

Included in GRADE tables or footnotes

- Hazell P, Mirzaie M (2013). Tricyclic drugs for depression in children and adolescents. Cochrane Database of Systematic Reviews.6:CD002317.

- Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents (Review). Cochrane Database of Systematic Reviews.11:CD004851.

- Spielmans GI and Gerwig K (2014). The Efficacy of Antidepressants on Overall Well-Being and Self-Reported Depression Symptom Severity in Youth: A Meta-Analysis. Psychotherapy and Psychosomatics.83:158–164.

Excluded from GRADE tables and footnotes

Hammad TA, Laughren T, Racoosin J (2006). Suicidality in pediatric patients treated with antidepressant drugs. Archives of General Psychiatry.63:332-339.
REASON FOR EXCLUSION: This review is older than Hetrick et al. (2012). See below for a narrative description.

Miller M, Swanson SA, Azrael D, Pate V, Sturmer T (2014). Antidepressant Dose, Age, and the Risk of Deliberate Self-harm. JAMA Internal Medicine.174(6):899-909.
REASON FOR EXCLUSION: This is a single observational study. See below for a narrative description.

Qin B, Zhang Y, Zhou X, Cheng P, Liu Y, Chen J, Fu Y, Luo Q, Xie P (2014). Selective Serotonin Reuptake Inhibitors Versus Tricyclic Antidepressants in Young Patients: A Meta-analysis of Efficacy and Acceptability. Clinical Therapeutics.36(7):1087-1095.
REASON FOR EXCLUSION: This review included only head-to-head comparisons between TCAs and SSRIs. See below for a narrative description.

Stevanovic D, Tadic I, Knez R (2014). Are antidepressants effective in quality of life improvement among children and adolescents? A systematic review. CNS Spectrum.19(2):134-41.
REASON FOR EXCLUSION: This review has no meta-analysis. See below for a narrative description.

Stone M, Laughren T, Jones ML, Levenson M, Holland CP, Hughes A, Hammad TA, Temple R, Rochester G (2009). Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ.339:b2880. doi:10.1136/bmj.b2880.
REASON FOR EXCLUSION: This review included only adult individuals. See below for a narrative description.

PICO Table

Population: Adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective				
Intervention	**Comparison**	**Outcome**	**Systematic reviews used for GRADE[1]**	**Relevant GRADE table**
Tricyclic or related	Placebo	Symptom reduction – response	Hazell and Mirzaie (2013):	Table 1

medications		(dichotomous outcome)	Analysis 2.3	
		Symptom reduction – mean improvement (continuous outcome)	Hazell and Mirzaie (2013): Analysis 2.4	Table 1
		Remission	No data	
		Functioning	No data	
		Remission	No data	
		Adverse effects of treatment – number of withdrawals (dropouts)	Hazell and Mirzaie (2013): Analysis 1.5 (children and adolescents considered together)	Table 1
		Adverse effects of treatment – suicidality	No data	
SSRIs and newer antidepressants	Placebo	Symptom reduction – response (dichotomous outcome)	Hetrick et al. (2012): Analysis 2.2	Table 2
		Symptom reduction – mean improvement (continuous outcome)	Hetrick et al. (2012): Analysis 2.1	Table 2
		Remission	No data	
		Functioning	Hetrick et al. (2012): Analysis 2.4 Spielmans and Gerwig (2014): Table 2	Table 2
		Adverse effects of treatment – number of withdrawals (dropouts)	Hetrick et al. (2012): Analysis 2.6	Table 2
		Adverse effects of treatment – suicidality	Hetrick et al. (2012): Analysis 2.5	Table 2
Paroxetine	Placebo	Symptom reduction – response (dichotomous outcome)	Hetrick et al. (2012): Analysis 1.2 (children and adolescents considered together)	Table 3
		Symptom reduction – mean improvement (continuous outcome)	Hetrick et al. (2012): Analysis 1.1 (children and adolescents considered together)	Table 3

		Remission	No data	
		Functioning	Hetrick et al. (2012): Analysis 1.5 (children and adolescents considered together)	Table 3
		Adverse effects of treatment – number of withdrawals (dropouts)	Hetrick et al. (2012): Analysis 1.8 (children and adolescents considered together)	Table 3
		Adverse effects of treatment – suicidality	Hetrick et al. (2012): Analysis 1.6 (children and adolescents considered together)	Table 3
Fluoxetine	Placebo	Symptom reduction – response (dichotomous outcome)	Hetrick et al. (2012): Analysis 1.2 (children and adolescents considered together)	Table 4
		Symptom reduction – mean improvement (continuous outcome)	Hetrick et al. (2012): Analysis 1.1 (children and adolescents considered together)	Table 4
		Remission	No data	
		Functioning	Hetrick et al. (2012): Analysis 1.5 (children and adolescents considered together)	Table 4
		Adverse effects of treatment – number of withdrawals (dropouts)	Hetrick et al. (2012): Analysis 1.8 (children and adolescents considered together)	Table 4
		Adverse effects of treatment – suicidality	Hetrick et al. (2012): Analysis 1.6 (children and adolescents considered together)	Table 4
Sertraline	Placebo	Symptom reduction – response (dichotomous outcome)	Hetrick et al. (2012): Analysis 1.2 (children and adolescents considered together)	Table 5
		Symptom reduction – mean improvement (continuous outcome)	Hetrick et al. (2012): Analysis 1.1 (children and adolescents considered together)	Table 5
		Remission	No data	
		Functioning	Hetrick et al. (2012): Analysis 1.5 (children and adolescents considered together)	Table 5

		Adverse effects of treatment – number of withdrawals (dropouts)	No data	
		Adverse effects of treatment – suicidality	Hetrick et al. (2012): Analysis 1.6 (children and adolescents considered together)	Table 5
Citalopram	Placebo	Symptom reduction – response (dichotomous outcome)	Hetrick et al. (2012): Analysis 1.2 (children and adolescents considered together)	Table 6
		Symptom reduction – mean improvement (continuous outcome)	Hetrick et al. (2012): Analysis 1.1 (children and adolescents considered together)	Table 6
		Remission	No data	
		Functioning	Hetrick et al. (2012): Analysis 1.5 (children and adolescents considered together)	Table 6
		Adverse effects of treatment – number of withdrawals (dropouts)	Hetrick et al. (2012): Analysis 1.8 (children and adolescents considered together)	Table 6
		Adverse effects of treatment – suicidality	Hetrick et al. (2012): Analysis 1.6 (children and adolescents considered together)	Table 6
Escitalopram	Placebo	Symptom reduction – response (dichotomous outcome)	Hetrick et al. (2012): Analysis 1.2 (children and adolescents considered together)	Table 7
		Symptom reduction – mean improvement (continuous outcome)	Hetrick et al. (2012): Analysis 1.1 (children and adolescents considered together)	Table 7
		Remission	No data	
		Functioning	Hetrick et al. (2012): Analysis 1.5 (children and adolescents considered together)	Table 7
		Adverse effects of treatment – number of withdrawals (dropouts)	Hetrick et al. (2012): Analysis 1.8 (children and adolescents considered together)	Table 7

		Adverse effects of treatment – suicidality	Hetrick et al. (2012): Analysis 1.6 (children and adolescents considered together)	Table 7

[1]Hazell and Mirzaie (2013) was selected because it is a recent Cochrane review on tricyclic medications for depression in children and adolescents. Hetrick et al. (2012) was selected because it is a recent Cochrane review on newer generation antidepressants for depressive disorders in children and adolescents, and it included functioning as an outcome. Spielmans and Gerwig (2014) was selected because it is a recent systematic review which has a specific focus on well-being including functioning as an outcome.

Narrative description of the studies that went into analysis

The reviews below describe *indirect* evidence because the population in the review covered *adolescents with depressive disorder,* rather than *adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.*

Hazell and Mirzaie (2013):
There are 14 relevant RCTs included in this Cochrane systematic review comparing the efficacy of orally administered TCAs with placebo in depressed people aged 6 to 18 years. Of these, eight trials targeted adolescents (aged 12 years and over), four trials targeted children (aged 11 years and under) and two trials involved participants spanning childhood and adolescence. Six 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. The treatment-placebo difference was statistically significant in two of eight studies. No overall difference was found for the primary outcome of response to treatment compared with placebo (RR 1.07; 95% CI; 0.91 to 1.26; 9 trials, N = 454). There was a small reduction in depression symptoms (SMD[i] -0.32, 95% CI -0.59 to -0.04; 13 trials, N = 533), but the evidence was of low quality. Subgroup analyses suggested a small reduction in depression symptoms among adolescents (SMD -0.45, 95% CI -0.83 to -0.007), and negligible change among children (SMD 0.15, 95% CI -0.34 to 0.64). Treatment with a tricyclic antidepressant caused more vertigo (RR 2.76, 95% CI 1.73 to 4.43; 5 trials, N = 324), orthostatic hypotension (RR 4.86, 95% CI 1.69 to 13.97; 5 trials, N = 324), tremor (RR 5.43, 95% CI 1.64 to 17.98; 4 trials, N = 308) and dry mouth (RR 3.35, 95% CI 1.98 to 5.64; 5 trials, N = 324) than did placebo, but no differences were found for other possible adverse effects. Wide CIs and the probability of selective reporting mean that there was very low-quality evidence for adverse events. There was heterogeneity across the studies in the age of participants, treatment setting, tricyclic medication administered and outcome measures. Statistical heterogeneity was identified for reduction in depressive symptoms, but not for rates of remission or response.

Hetrick et al. (2012):
This review contained 19 trials (with a total of 3353 participants) testing the effectiveness of newer generation antidepressants. Published and unpublished RCTs, cross-over trials and cluster trials comparing a newer generation antidepressant with a placebo in children and adolescents aged 6 to 18 years old and diagnosed with a depressive disorder were eligible for inclusion. There were six trials involving adolescents only with an age

range of 12 to 18 years and 13 trials involving children and adolescents. In the SSRI class, there were four trials of paroxetine, five trials of fluoxetine, two trials of citalopram, two trials of escitalopram oxalate (the therapeutically active component of citalopram) and two trials of sertraline. All trials excluded young people at high risk of suicide and many co-morbid conditions and the participants are likely to be less unwell than those seen in clinical practice. Overall, there was evidence that those treated with an antidepressant had lower depression severity scores and higher rates of response/remission than those on placebo. However, the size of these effects was small with a reduction in depression symptoms of 3.51 on a scale from 17 to 113 (14 trials; N = 2490; MD[ii] -3.51; 95% CI -4.55 to - 2.47). Remission rates increased from 380 per 1000 to 448 per 1000 for those treated with an antidepressant. There was evidence of an increased risk (58%) of suicide-related outcome for those on antidepressants compared with a placebo (17 trials; N = 3229; RR 1.58; 95% CI 1.02 to 2.45). This equates to an increased risk in a group with a median baseline risk from 25 in 1000 to 40 in 1000. Where rates of adverse events were reported, this was higher for those prescribed an antidepressant. There was no evidence that the magnitude of intervention effects (compared with placebo) were modified by individual medication class.

Spielmans and Gerwig (2014):
This review included eight randomized trials comparing antidepressants vs. placebo in children and adolescents and employing outcome measures assessing quality of life, functioning and overall well-being. The review found a nonsignificant difference between second-generation antidepressants and placebo in terms of self-reported depressive symptoms (k = 6 trials, g = 0.06, p = 0.36). Further, pooled across measures of quality of life, global mental health, self-esteem, and autonomy, antidepressants yielded no significant advantage over placebo (k = 3 trials, g = 0.11, p = 0.13).

GRADE Tables

Table 1 . TCAs or related medications vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli
Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of TCAs or related medications compared to placebo?
Bibliography: Hazell P, Mirzaie M (2013). Tricyclic drugs for depression in children and adolescents. Cochrane Database of Systematic Reviews.6:CD002317.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tricyclic or related medications	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – Response (dichotomous outcome)												
6[1]	Randomized	Serious[2]	No serious	Serious [8]	No serious	None	88/166	88/173	RR 1.01 (0.85 to	5 more per 1000 (from 76 fewer to 97	⊕⊕OO	CRITICAL

	trials		inconsistency		imprecision		(53%)	(50.9%)	1.19)	more)	LOW	
Symptom reduction – Mean improvement (continuous outcome) (better indicated by lower values)												
8[3]	Randomized trials	Serious[2]	Serious[4]	Serious [8]	No serious imprecision	None	201	213	-	SMD 0.45 lower (0.83 to 0.07 lower)	⊕OOO VERY LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Adverse effects of treatment – Number of withdrawals (dropouts)												
8[5]	Randomized trials	No serious risk of bias	No serious inconsistency[6]	Serious [8]	Serious[7]	None	74/237 (31.2%)	45/225 (20%)	RR 1.48 (0.94 to 2.31)	96 more per 1000 (from 12 fewer to 262 more)	⊕⊕OO LOW	IMPORTANT
Adverse effects of treatment – Suicidality (better indicated by lower values)												
0	No evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL

[1] Analysis 2.3 of Hazell and Mirzaie (2013).
[2] Dropout rate is approximately 30% in some studies; dropouts are not similarly distributed between treatment arms in two studies.
[3] Analysis 2.4 of Hazell and Mirzaie (2013).
[4] I-squared=65%
[5] Analysis 1.5 of Hazell and Mirzaie (2013).
[6] Children and adolescents considered together.
[7] Confidence interval ranges from almost no difference to substantial harm associated with tricyclic medications.
[8] The review covered adolescents with depressive disorder and not adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.

[2015]

Table 2. SSRIs and newer antidepressant medications vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli

Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of SSRIs and newer antidepressant medications compared to placebo?

Bibliography:

- Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.
- Spielmans GI and Gerwig K (2014). The Efficacy of Antidepressants on Overall Well-Being and Self-Reported Depression Symptom Severity in Youth: A Meta-Analysis. Psychotherapy and Psychosomatics.83:158–164.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs and newer ADs[iii]	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – Response (dichotomous outcome)												
7[1]	Randomized trials	Serious[2]	No serious inconsistency	Serious [11]	No serious imprecision	None[3]	319/617 (51.7%)	239/564 (42.4%)	RR 1.13 (1.02 to 1.26)	55 more per 1000 (from 8 more to 110 more)	⊕⊕OO LOW	CRITICAL
Symptom reduction – Mean improvement (continuous outcome) (better indicated by lower values)												
10[4]	Randomized trials	Serious[2]	No serious inconsistency	Serious [11]	No serious imprecision	None[3]	0[5]	-	-	MD 4.21 lower (5.5 to 2.92 lower)	⊕⊕OO LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by lower values)												
5[6]	Randomized trials	Serious[2]	No serious inconsistency	Serious [11]	No serious imprecision	None	0[5]	-	-	MD 2.82 higher (1.17 to 4.47 higher)[7]	⊕⊕OO LOW	CRITICAL

Adverse effects of treatment - Number of withdrawals (dropouts)												
6[8]	Randomizedtrials	Serious[2]	No serious inconsistency	Serious [11]	No serious imprecision	None	502/711 (70.6%)	392/616 (63.6%)	RR 1.11 (1.04 to 1.19)	70 more per 1000 (from 25 more to 121 more)	⊕⊕OO LOW	IMPORTANT
Adverse effects of treatment – Suicidality												
10[9]	Randomized trials	Serious[2]	No serious inconsistency	Serious [11]	Serious[10]	None[3]	66/881 (7.5%)	39/786 (5%)	RR 1.47 (0.99 to 2.19)	23 more per 1000 (from 0 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL

[1] Analysis 2.2.2 of Hetrick et al. (2012).
[2] The attrition rate for the included trials varied between 11% and 82% in the control groups, and 14% and 58% in the intervention groups. Most of these trials were judged to be at low risk of bias.
[3] The funnel plots for the outcomes remission and suicide-related behaviour were not suggestive of small study effects. Additionally, the contour-enhanced funnel plots did not indicate that statistically significant results were more likely to be reported (i.e., publication bias).
[4] Analysis 2.1.2 of Hetrick et al. (2012).
[5] Not reported.
[6] Analysis 2.4.2 of Hetrick et al. (2012).
[7] In addition to these negative findings, Spielmans and Gerwig (2014) found no evidence that antidepressant medications offer any sort of clinically meaningful benefit for youth on self-report measures of quality of life, global mental health or parent reports of autonomy.
[8] Analysis 2.6.2 of Hetrick et al. (2012).
[9] Analysis 2.5.2 of Hetrick et al. (2012).
[10] Confidence interval ranges from no difference to substantial harm associated with antidepressant exposure.
[11] The review covered adolescents with depressive disorder and not adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.

Table 3. Parozetine vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli
Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of paroxetine compared to placebo?
Bibliography: Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetine	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – Response (dichotomous outcome)												
4[1]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[4]	202/397 (50.9%)	133/307 (43.3%)	RR 1.12 (0.90 to 1.38)	52 more per 1000 (from 43 fewer to 165 more)	⊕OOO VERY LOW	CRITICAL
Symptom reduction – Mean improvement (continuous outcome) (better indicated by lower values)												
2[5]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	Serious[6]	None[4]	0[7]	-	-	MD 1.18 lower (6.29 lower to 3.92 higher)	⊕OOO VERY LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by higher values)												
1[8]	Randomized trials	Serious[9]	No serious inconsistency[10]	Serious	Serious[11]	None[4]	0[7]	-	-	MD 1.60 higher (2.48 lower to 5.68 higher)	⊕OOO VERY LOW	CRITICAL

Adverse effects of treatment – Number of withdrawals (dropouts)												
4[12]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[4]	293/405 (72.3%)	206/309 (66.7%)	RR 1.11 (0.98 to 1.25)	73 more per 1000 (from 13 fewer to 167 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects of treatment – Suicidality												
4[13]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	Serious[6]	None[4]	20/397 (5%)	9/305 (3%)	RR 1.57 (0.46 to 5.31)	17 more per 1000 (from 16 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL

[1] Analysis 1.2.1 of Hetrick et al. (2012).
[2] Attrition rate is approximately 30% in some studies.
[3] Children and adolescents considered together rather than adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.
[4] The funnel plot analysis did not indicate that statistically significant results were more likely to be reported (i.e., publication bias). Unpublished studies included.
[5] Analysis 1.1.1 of Hetrick et al. (2012).
[6] Confidence interval ranges from substantial benefit to substantial harm.
[7] Not reported.
[8] Analysis 1.5.1 of Hetrick et al. (2012).
[9] Attrition rate is approximately to 30%.
[10] Only one study included in the analysis.
[11] Only one study included in the analysis. Confidence interval ranges from substantial benefit to substantial harm.
[12] Analysis 1.8.1 of Hetrick et al. (2012).
[13] Analysis 1.6.1 of Hetrick et al. (2012).

[2015]

Table 4. Fluzetine vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli
Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of fluoxetine compared to placebo?
Bibliography: Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – response (dichotomous outcome)												
4[1]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[4]	89/273 (32.6%)	56/270 (20.7%)	RR 1.47 (1.03 to 2.08)	97 more per 1000 (from 6 more to 224 more)	⊕OOO VERY LOW	CRITICAL
Symptom reduction – mean improvement (continuous outcome) (Better indicated by lower values)												
3[5]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[4]	0[6]	-	-	MD 5.63 lower (7.39 to 3.86 lower)	⊕OOO VERY LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by higher values)												
2[7]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[4]	0[6]	-	-	MD 3.08 higher (0.14 to 6.02 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects of treatment - number of withdrawals (dropouts)												

2[8]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[4]	141/218 (64.7%)	119/222 (53.6%)	RR 1.19 (1.05 to 1.35)	102 more per 1000 (from 27 more to 188 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects of treatment – suicidality												
3[9]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	Serious[10]	None[4]	20/266 (7.5%)	11/270 (4.1%)	RR 1.77 (0.85 to 3.69)	31 more per 1000 (from 6 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL

[1] Analysis 1.2.2 of Hetrick et al. (2012).
[2] Attrition rate unequally distributed between treatment arms.
[3] Children and adolescents considered together rather than adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.
[4] The funnel plot analysis did not indicate that statistically significant results were more likely to be reported (i.e., publication bias). Unpublished studies are included.
[5] Analysis 1.1.2 of Hetrick et al. (2012).
[6] Not reported.
[7] Analysis 1.5.2 of Hetrick et al. (2012).
[8] Analysis 1.8.2 of Hetrick et al. (2012).
[9] Analysis 1.6.2 of Hetrick et al. (2012).
[10] Confidence interval ranges from no difference to substantial harm associated with fluoxetine exposure.

[2015]

Table 5. Sertraline vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli
Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of sertraline compared to placebo?
Bibliography: Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – response (dichotomous outcome)												
1[1]	Randomized trials	Serious[2]	no serious inconsistency[3]	Very serious[4]	Serious[5]	None[6]	128/185 (69.2%)	106/179 (59.2%)	RR 1.17 (1 to 1.36)	101 more per 1000 (from 0 more to 213 more)	⊕OOO VERY LOW	CRITICAL
Symptom reduction – mean improvement (continuous outcome) (better indicated by lower values)												
2[7]	Randomized trials	Serious[2]	no serious inconsistency	Very serious[4]	No serious imprecision	None[6]	0[8]	-	-	MD 3.52 lower (6.64 to 0.40 lower)	⊕OOO VERY LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by higher values)												
1[9]	Randomized trials	Serious[2]	no serious inconsistency[3]	Very serious[4]	Very serious[5]	None[6]	0[8]	-	-	MD 1.31 higher (1.61 lower to 4.23 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects of treatment - number of withdrawals (dropouts) (better indicated by lower values)												

0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects of treatment – suicidality												
1[10]	Randomized trials	Serious[2]	No serious inconsistency[3]	Very serious[4]	Serious[11]	None[6]	6/189 (3.2%)	2/187 (1.1%)	RR 2.97 (0.61 to 14.52)	21 more per 1000 (from 4 fewer to 145 more)	⊕OOO VERY LOW	

[1] Analysis 1.2.3 of Hetrick et al. (2012).
[2] Dropout rate unequally distributed between treatment arms.
[3] Only one study included in the analysis.
[4] Children and adolescents considered together rather than adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.
[5] Only one study included in the analysis and confidence interval ranges from no difference to substantial benefit associated with sertraline.
[6] The funnel plot analysis did not indicate that statistically significant results were more likely to be reported (i.e., publication bias). Unpublished studies are included.
[7] Analysis 1.1.3 of Hetrick et al. (2012).
[8] Not reported.
[9] Analysis 1.5.3 of Hetrick et al. (2012).
[10] Analysis 1.6.3 of Hetrick et al. (2012).
[11] Confidence interval ranges from almost no difference to substantial harm associated with sertraline.

[2015]

Table 6. Citalopram vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli
Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of citalopram compared to placebo?
Bibliography: Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Citalopram	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – response (dichotomous outcome)												
2[1]	Randomized trials	Serious[2]	Serious[3]	Very serious[4]	Serious[5]	None[6]	72/210 (34.3%)	60/197 (30.5%)	RR 1.16 (0.71 to 1.89)	49 more per 1000 (from 88 fewer to 271 more)	⊕OOO VERY LOW	CRITICAL
Symptom reduction – mean improvement (continuous outcome) (better indicated by lower values)												
1[7]	Randomized trials	Serious[2]	No serious inconsistency[8]	Very serious[4]	Serious[5]	None[6]	0[9]	-	-	MD 2.90 lower (7.77 lower to 1.97 higher)	⊕OOO VERY LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by higher values)												
1[10]	Randomized trials	Serious[2]	No serious inconsistency[8]	Very serious[4]	Serious[11]	None[6]	0[9]	-	-	MD 2.50 higher (1.52 lower to 6.52 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects of treatment - number of withdrawals (dropouts)												

2[12]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[4]	Serious[13]	None[6]	166/210 (79%)	138/197 (70.1%)	RR 1.13 (1 to 1.29)	91 more per 1000 (from 0 more to 203 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects of treatment – suicidality												
2[14]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[4]	Very serious[15]	None[6]	17/213 (8%)	10/205 (4.9%)	RR 1.53 (0.55 to 4.27)	26 more per 1000 (from 22 fewer to 160 more)	⊕OOO VERY LOW	

[1] Analysis 1.2.4 of Hetrick et al. (2012).
[2] High dropout rates.
[3] I-squared=64%
[4] Children and adolescents considered together rather than adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.
[5] Confidence interval ranges from substantial benefit with citalopram to substantial benefit with placebo.
[6] The funnel plot analysis did not indicate that statistically significant results were more likely to be reported (i.e., publication bias). Unpublished studies are included.
[7] Analysis 1.1.4 of Hetrick et al. (2012).
[8] Only one study included in the analysis.
[9] Not reported.
[10] Analysis 1.5.4 of Hetrick et al. (2012).
[11] Confidence interval ranges from almost no difference to substantial benefit associated with citalopram.
[12] Analysis 1.8.3 of Hetrick et al. (2012).
[13] Confidence interval ranges from almost no difference to substantial harm associated with citalopram.
[14] Analysis 1.6.4 of Hetrick et al. (2012).
[15] Confidence interval ranges from substantial harm associated with placebo to substantial harm associated with citalopram.

Table 7. Escitalopram vs. placebo for treatment of moderate-severe depressive disorder in adolescents

Authors: C Barbui and I Bighelli

Question: In adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective, what is the effectiveness and safety of escitalopram compared to placebo?

Bibliography: Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Placebo	Relative (95% CI)	Absolute		
Symptom reduction – response (dichotomous outcome)												
2[1]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	Serious[4]	None[5]	123/283 (43.5%)	106/289 (36.7%)	RR 1.19 (0.97 to 1.45)	70 more per 1000 (from 11 fewer to 165 more)	⊕OOO VERY LOW	CRITICAL
Symptom reduction – mean improvement (continuous outcome) (better indicated by lower values)												
2[6]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[5]	0[7]	-	-	MD 2.67 lower (4.85 to 0.48 lower)	⊕OOO VERY LOW	CRITICAL
Remission (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Functioning (better indicated by higher values)												
2[8]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[5]	0[7]	-	-	MD 2.28 higher (0.23 to 4.32 higher)	⊕OOO VERY LOW	CRITICAL

Adverse effects of treatment - number of withdrawals (dropouts)												
2[9]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	No serious imprecision	None[5]	211/285 (74%)	208/290 (71.7%)	RR 1.03 (0.94 to 1.14)	22 more per 1000 (from 43 fewer to 100 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects of treatment – suicidality												
2[10]	Randomized trials	Serious[2]	No serious inconsistency	Very serious[3]	Serious[11]	None[5]	15/285 (5.3%)	17/290 (5.9%)	RR 0.91 (0.47 to 1.76)	5 fewer per 1000 (from 31 fewer to 45 more)	⊕OOO VERY LOW	CRITICAL

[1] Analysis 1.2.5 of Hetrick et al. (2012).
[2] High dropout rates.
[3] Children and adolescents considered together rather than adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective.
[4] Confidence interval ranges from no difference to substantial benefit associated with escitalopram.
[5] The funnel plot analysis did not indicate that statistically significant results were more likely to be reported (i.e., publication bias). Unpublished studies are included.
[6] Analysis 1.1.5 of Hetrick et al. (2012).
[7] Not reported.
[8] Analysis 1.5.5 of Hetrick et al. (2012).
[9] Analysis 1.8.4 of Hetrick et al. (2012)..
[10] Analysis 1.6.5 of Hetrick et al. (2012).
[11] Confidence interval ranges from substantial harm associated with placebo to substantial harm associated with escitalopram.

Additional evidence not mentioned in GRADE tables

TCAs vs. SSRIs

Qiu et al. (2014) performed a meta-analysis comparing the efficacy and acceptability of SSRIs vs. TCAs in depressed children, adolescents and young adults, which included 5 trials with a total of 422 adolescents. The main findings were as follows:

- SSRIs were significantly more effective than TCAs in primary efficacy (SMD - 0.52; 95% CI - 0.81 to -0.24);
- Adolescents taking SSRIs had a significantly greater response to depressive symptoms than adolescents taking TCAs (RR 1.55; 95% CI 1.04 to 2.29);

- On an individual SSRI basis, fluoxetine had a significantly greater efficacy than TCAs (SMD -0.82; 95% CI -1.34 to -0.29);
- Significantly more adolescents taking TCAs discontinued treatment than adolescents taking SSRIs (35.8% vs. 25.1%; RR 0.70; 95% CI 0.52 to 0.93).

These findings indicate that SSRI therapy holds a superior efficacy and is better tolerated compared with TCA therapy in adolescents. Although there were no significant differences in suicide-related outcomes, caution is required with SSRI use.

Sub-group analyses revealed that the superior efficacy of SSRI therapy is more attributable to fluoxetine than paroxetine.

Antidepressant medications and quality of life

Stevanovic et al. (2014) reviewed evidence on whether antidepressant treatment improves quality of life (QOL) among children and adolescents with depressive or anxiety disorders. Five clinical trials were included in this review: four trials with major depressive disorder (MDD) and one trial with social anxiety disorder (SAD). QOL was measured with the following instruments: EQ-5D VAS (The Euro QOL measure), PQ-LES-Q5 (Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire), Y-QOL-R5 (Youth Quality of Life Instrument–Research Version). Antidepressant medications in these trials had minor positive effects on QOL. Although fluoxetine with cognitive behavioural therapy (CBT) or sertraline monotherapy were shown to have some potential to improve QOL, this systematic review found inconclusive evidence that antidepressant treatments improve QOL among children and adolescents with depressive or anxiety disorders.

Antidepressant medications and suicide

In May 2007, the Food and Drug Administration (FDA) ordered that all AD medications carry an expanded black-box warning incorporating information about an increased risk of suicidal symptoms in young adults aged 18 to 24 years. The warning was based on the results of an FDA meta-analysis of 372 placebo-controlled AD trials with almost 100,000 participants (Stone et al., 2009). On the basis of this analysis the relationship between AD treatment and the incidence of reported suicidal behaviour in clinical trials was strongly related to age. The meta-analysis found, elevated risk associated with medication treatment relative to placebo in subjects younger than 25; neutral risk in subjects aged 25 to 64 years (but reduced if suicidal behaviour and ideation are considered together); and reduced risk in subjects aged 65 years and older.

Another FDA meta-analysis suggested that the rate of suicidal ideation and behaviour in children randomized to AD medications was twice that of children randomized to placebo (Hammad et al., 2006).

Although the mechanism by which AD use may increase the risk of suicide is unknown, it has been hypothesized that adverse effects may play a key role, including akathisia, insomnia and panic attacks, as well as an early energizing effect that might allow adolescents with depressive disorder to act on suicidal impulses. Considering that these adverse effects are dose-related, it has also been hypothesized that the risk of suicidal behaviour is

similarly related to AD dose. This research question was addressed by Miller et al. (2004), who carried out a propensity score-matched cohort study based on observational health care utilization data. This study involved 162,625 people aged 10 to 64 years with a depressive disorder diagnosis who initiated therapy with citalopram, sertraline or fluoxetine. According to AD dose prescribed among AD initiators, adolescents were assigned to a modal dose category or to a high-dose category. The modal daily dose for citalopram, sertraline and fluoxetine were 20 mg/day, 50 mg/day and 20 mg/day, respectively. Study follow-up began on the day after initiation of the first AD therapy, with the outcome of interest centred on the first occurrence of acts of deliberate self-harm (DSH). Adolescents were divided into two age groups, ages 10-24 years vs. ages 25-64 years, with group age range selection guided by age-related risk of suicidal behaviour identified in the FDA meta-analyses. The study found that the rate of DSH in the 10-24 years age group who initiated high-dose therapy was approximately twice as high as among matched adolescents initiating modal-dose therapy (hazard ratio 2.2; 95% CI from 1.6 to 3.0). By contrast, no effect was detected in the 25-64 years age group.

The finding that high initial AD dose leads to an increased risk for DSH is a new and original finding that has substantial implications for everyday clinical practice because it clearly demonstrates that AD treatment should not be started with greater than modal doses.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Outcome	**Adolescents with moderate-severe depression** *(Number of studies, RR or MD [95% CI], findings and quality)*		**Children and adolescents with moderate-severe depression** *(Number of studies, RR or MD [95% CI], findings and quality)*				
	TCA or related	**SSRIs and newer**	**Paroxetine**	**Fluoxetine**	**Sertraline**	**Citalopram**	**Escitalopram**
Response – dichotomous outcome	6 studies, RR 1.01 (0.85 to 1.19), No difference, LOW	7 studies, RR 1.13 (1.02 to 1.26), In favour of SSRI, LOW	4 studies, RR 1.12 (0.90 to 1.38), In favor of paroxetine, VERY LOW	4 studies, RR 1.47 (1.03 to 2.08), In favor of fluoxetine, VERY LOW	1 study, RR 1.17 (1.00 to 1.36), In favor of sertraline, VERY LOW	2 studies, RR 1.16 (0.71 to 1.89), No difference, VERY LOW	2 studies, RR 1.19 (0.97 to 1.45), No difference, VERY LOW
Response – continuous outcome	8 studies, SMD -0.45 (-0.83 to -0.07),	10 studies, MD -4.21 (-5.50 to -2.92),	2 studies, MD -1.18 (-6.29 to 3.92),	3 studies, MD -5.63 (-7.39 to -3.86)	2 studies, MD -3.52 (-6.64 to -0.40),	1 study, MD -2.90 (-7.77 to 1.97),	2 studies, MD -2.67 (-4.85 to - 0.48),

	In favor of TCA, VERY LOW	In favor of SSRI, LOW	No difference, VERY LOW	In favor of fluoxetine, VERY LOW	In favor of sertraline, VERY LOW	No difference, VERY LOW	In favor of escitalopram, VERY LOW
Remission	_____	_____	_____	_____	_____	_____	_____
Functioning	_____	5 studies, SMD 2.82 (1.17 to 4.47), In favor of placebo, LOW*	1 study, MD 1.60 (-2.48 to 5.68), No difference, VERY LOW	2 studies, MD 3.08 (0.14 to 6.02), In favor of placebo, VERY LOW	1 study, MD 1.31 (-1.61 to 4.23), No difference, VERY LOW	1 study, MD 2.50 (-1.52 to 6.52), No difference, VERY LOW	2 studies, MD 2.28 (0.23 to 4.32), In favor of placebo, VERY LOW
Study withdrawals (dropouts)	8 studies, RR 1.48 (0.94 to 2.31), No difference, LOW	6 studies, RR 1.11 (1.04 to 1.19), In favor of placebo, LOW	4 studies, RR 1.11 (0.98 to 1.25), No difference, VERY LOW	2 studies, RR 1.19 (1.05 to 1.35), In favor of placebo, VERY LOW	_____	2 studies, RR 1.13 (1.00 to 1.29), In favor of placebo, VERY LOW	2 studies, RR 1.03 (0.94 to 1.14), No difference, VERY LOW
Adverse effects - suicidality	_____	10 studies, RR 1.47 (0.99 to 2.19), No difference, VERY LOW	4 studies, RR 1.57 (0.46 to 5.31), No difference, VERY LOW	3 studies, RR 1.77 (0.85 to 3.69), No difference, VERY LOW	1 study, RR 2.97 (0.61 to 14.52), No difference, VERY LOW	2 studies, RR 1.53 (0.55 to 4.27), No difference, VERY LOW	2 studies, RR 0.91 (0.47 to 1.76), No difference, VERY LOW

*In addition to these negative findings in terms of functioning, the review by Spielmans and Gerwig (2014) found no evidence that antidepressant medications offer any sort of clinically meaningful benefit for youth on self-report measures of quality of life, global mental health or parent reports of autonomy.

Evidence to recommendation table

Benefits	In terms of treatment response (a dichotomous outcome), there is low quality evidence suggesting there is unlikely to be a clinically important difference between TCAs and placebo. However, in terms of depressive symptoms (a continuous outcome), there is very low quality evidence favouring TCAs over placebo. In terms of treatment response and symptom reduction, there is low quality evidence favouring SSRIs over placebo. It is uncertain if the difference is clinically significant. Among the SSRIs, there was low quality evidence that fluoxetine, when compared with placebo, produced clinically significant benefits in terms of treatment response and symptom reduction.
Harms	In terms of study withdrawals (dropouts), there is very low quality evidence suggesting that there is unlikely to be a clinically important difference between TCAs and placebo. In terms of acceptability profile, there is low quality evidence that SSRIs increase risk of withdrawal due to adverse effects. In terms of suicide-related outcomes, there is very low quality evidence pointing to an increased risk associated with SSRIs, while the confidence interval does not rule out the possibility of no difference between SSRIs and placebo. There is also very low quality evidence for fluoxetine alone and sertraline.
Summary of the quality of evidence	The evidence quality for the comparisons made in this profile is either low or very low, depending on the comparison. In this population of adolescents with moderate-severe depression, the evidence suggests that benefits of fluoxetine treatment outweighs associated harms.

Value and preferences	
In favour	Clinicians in non-specialized care may prefer to offer antidepressant medication instead of psychological treatment because these clinicians often do not have sufficient time to provide evidence-based psychological interventions, such as cognitive behavioural therapy.

Against	In situations where adolescents are exposed to severe ongoing social stressors (e.g., bullying, severe family disputes), it is preferable to try to address the social stressors before initiating antidepressant treatment. Individual preferences for antidepressant medications and treatment options vary within adolescent populations. Weight-related side effects can influence the acceptability of-, and preference for antidepressant medications, especially among girls. Many clinicians prefer to avoid psychoactive medication in adolescents due to developmental concerns. Children and adolescents may also be more likely to experience adverse health consequences after treatment involving psychoactive medication. Furthermore, unlike psychological treatment approaches such as cognitive behavioural therapy, antidepressant medication treatment does not support the development of necessary coping skills that adolescents need to improve their capacity to manage distress and difficult situations.
Uncertainty or variability?	There is considerable variability in values and preferences.

Feasibility (including resource use considerations)	Clinicians need to be trained in antidepressant medication administration, including side-effects monitoring. Both generic TCAs and many generic SSRIs are associated with low acquisition costs. In many LAMICs, there is no continuous availability of specific psychotropic medications in non-specialized health care settings. In many LAMICs, there is limited availability of supportive supervision of mental health care in non-specialized health care settings.

	Fluoxetine (but no other SSRIs) is included in the WHO list of essential medicines for the treatment of depressive disorders in older children and adolescents, aged 9 years and up.
Uncertainty or variability?	There is considerable variability in feasibility.

Recommendation and remarks

Recommendation

When psychosocial interventions prove ineffective, fluoxetine (but not other Selective Serotonin Reuptake Inhibitors or Tricyclic Antidepressants) may be offered in adolescents with moderate-severe depressive episode/disorder. The intervention should only be offered under supervision of a specialist.

Rationale: Although in the long-term there are safety and tolerability concerns associated with antidepressant treatment in this age group, the evidence suggests that fluoxetine is an SSRI with a favourable benefit to risk ratio. Clinicians need to be trained in prescribing antidepressants, including side-effects monitoring.

Remarks

Within the context of this recommendation, specialists include (a) psychiatrists and neuro-psychiatrists (b) paediatricians and family physicians with post-degree training in the management of adolescent depression.

The decision to prescribe fluoxetine should be made together with the adolescent, in line with the evolving capacity of the adolescent.

Adolescents on fluoxetine should be monitored closely for suicide ideas/behaviour.

Fluoxetine treatment should not be started with greater than minimal effective doses. It is suggested to initiate treatment

with 10 mg once daily and increase to 20 mg after 1 – 2 weeks (maximum dose 20 mg). If no response in 6 – 12 weeks or partial response in 12 weeks, re-consult a specialist.

In countries that only have 20mg capsules that cannot be split in half, due to the long half-life of fluoxetine, it is possible to prescribe fluoxetine 20mg every other day (equivalent to initial dose of 10mg/day).

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate □ Low **X Very low**
Balance of benefits versus harms	□ Benefits clearly outweigh harms **X Benefits and harms are balanced** □ Potential harms clearly outweigh potential benefits
Values and preferences	□ No major variability **X Major variability**
Resource use	□ Less resource-intensive **X More resource-intensive**
Strength	**CONDITIONAL**

OTHER REFERENCES

Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews.11:CD004851.

Qiu BY, Qiao JX, Yong J (2014). Meta-analysis of selective serotonin reuptake inhibitors (SSRIs) compared to tricyclic antidepressants (TCAs) in the efficacy and safety of anti-derprssion therapy in Parkinson's disease patients. Iranian Journal of Pharmacology Research.13(4):1213-1219.

[i] Standardised mean difference (SMD)
[ii] Mean difference (MD)
[iii] Antidepressant (AD)