Application for updating fluoxetine age restriction
for the treatment of depression
from > 8 years to >12 years

Submitted by Mental Health: Evidence and Research
World Health Organization, Geneva
1. **Summary statement of the proposal for inclusion, change or deletion**

Currently fluoxetine is available both on the Essential Medicine List of children and in “Table 1” with an age restriction of >8 years to be used as a complementary medicine.

Depression is uncommon in early childhood and the main increase in prevalence happens in adolescence or later. Social and familial factors play a major role in depression of children and there are effective psychological and social interventions for the prevention and treatment of depression in children. Taking into consideration the lower incidence and prevalence of depression in younger children, the evidence reviews on the effectiveness or adverse effects of the medicine for younger age group, the realities of child mental health services in many low resource settings which might favour over-prescription, and the overall risk-benefit aspects; we suggest to increase of the age limit from >8 years to >12 years.

2. **Name of the focal point in WHO submitting or supporting the application (where relevant)**

Dr M.Taghi Yasamy, Medical Officer, Department of Mental Health and Substance Abuse

3. **Name of the organization(s) consulted and/or supporting the application**

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4. **International Nonproprietary Name (INN, generic name) of the medicine**

Fluoxetine

5. **Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

Not applicable

6. **International availability - sources, if possible manufacturers and trade names**

Not applicable

7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group**

Application is requested as an individual medicine
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Prevalence of depression is lower in childhood and increases over time. It appears to be rare in children younger than six years and of lower incidence before adolescence (1). In a meta-analysis of twenty-six studies including 60,000 observations on children, overall prevalence estimates for children under 13 years old was 2.8% (SE=0.5%) and for those between 13–18 years old it was 5.6% (SE=0.3%) which is close to adult figures (2). A sharp increase in incidence after childhood has been described(3).

Mental disorders including depression remain under-treated especially in low and middle income countries. In a WHO study in 42 countries, the median estimated one-year treated prevalence of all mental disorders for children and adolescents is 159 per 100,000 population compared to a treated prevalence of 664 per 100,000 for the adult population (4). Treatment gap for depression across all ages is overall about 50% in high income and 70% in low and middle income countries which in some countries reaches 90% (5,6).

The quality of treatment of depression in children is extremely important. The presentation of depression is often more complex in children as compared with adults. Many children and adolescents with depression present with irritability, bodily complaints or problems of behaviour or conduct (7). Because of their limited language abilities, the source of information is usually a parent, a teacher, another child etc, and there is not sufficient data on direct screening of depression in children (8). Depression in children is more often than not related to life adversities and maltreatment than to biological factors (9,10) and requires psychosocial and parental interventions (11). A recent meta-analysis reconfirmed that depression consequent to child maltreatment can take a different course and is more difficult to treat (12). Children – who are still in development - are also more susceptible to adverse effects of medicines and many second generation antidepressants have been shown to have an unfavourable risk benefit profile for children and adolescents than for adults. This includes increased suicidal behavior and ideas (13). Antidepressants have been largely overused in children especially after the advent of SSRIs (14). There is a concerning history of people receiving anti-depressants without indication (15, 16).

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

WHO’s mental health Gap Action Programme Intervention Guide (mhGAP-IG) was published in 2010 based on WHO guidelines, which were based on review of a series of evidence reviews conducted in 2009 (see http://www.who.int/entity/mental_health/mhgap/evidence/child/q10/en/index.html). The Guideline Development Group came up with the following strong recommendation:
“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.” (17,18).

Then it adds a standard (weak) recommendation:

“Fluoxetine, but not Tricyclic antidepressants (TCA) or other Selective serotonin reuptake inhibitors (SSRI), may be considered as one possible treatment of adolescents with depressive episode in non-specialist settings. Adolescents on fluoxetine should be monitored closely for suicide ideas/behaviour. For all adolescents on fluoxetine, support and supervision from a mental health specialist should be obtained, if available.”

10. Summary of comparative effectiveness in a variety of clinical settings:

The mhGAP guideline development group concluded the following (see Appendix 1 for more details, also available on WHO website) (15):

“In children 6-12 years of age with depressive episode/disorder... 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.”

The rest of the evidence profile elaborated on safety concerns, difficulty to differentiate clinical depressive disorder from transient reaction and the risk of medicalization of a social problem. Also the facts that children are still in development, cultural issues and possibility of incorrect diagnosis were highlighted in the evidence profile. For the above reasons, the GDG came up with a STRONG recommendation to set the limit of 12 years as mentioned above.

FDA
Fluoxetine is the only medication approved by the FDA for treating depression in children 8 years and older. In December 2006, the FDA’s Psychopharmacologic Drugs Advisory Committee asked for labeling changes and to inform health care professionals about “the increased risk of suicidality in younger adults using antidepressants” (17). The black box warning also notes that children and adolescents under SSRI medications should be closely monitored especially during the first four weeks of treatment. It also mentioned that SSRI medications “…usually have few side effects in children and adolescents, but for unknown reasons, they may trigger agitation and abnormal behavior in certain individuals . . .”. FDA included fluoxetine among other SSRIs to be included in the labeling changes for the medications despite agreement to approve it for use in children and adolescents (17).

NICE guidelines

NICE has adopted a cautious approach in 2005 and did not recommend medicines for the treatment of moderate to severe depression in young people unless the following conditions are met. It recommends that after intensively reviewing the case, they should offer a specific psychological therapy for at least 3 months. Then if depression still unresponsive to treatment after 4-6 sessions, to carry out a multidisciplinary review. Then they suggest to consider two options: alternative or perhaps additional psychological therapy for the parent and other family members and the patient and then comes considering medication. They suggest that for young people 12-18 years to offer fluoxetine in addition to psychological therapy and for children aged 5-11 years to “cautiously” consider the addition of fluoxetine. They mention that “evidence for its effectiveness in this age group is not established” (20).

Systematic reviews since mhGAP evidence review of 2009:

- Williams SB et al 2009 (21). They reviewed all clinical trials with fair and good quality on screening, psychotherapy and SSRIs for children age (7-18) in primary care. Unfortunately the age range was wide and only one trial focused on age 9-12 which was on group psychotherapy and not applicable to our purpose.

- Hetrick SE et al, 2012 published their updated Cochrane Review on “Newer generation antidepressants for depressive disorders in children and adolescents” (22). We had reviewed their previous systematic review in 2009 at times of the mhGAP guidelines development. In 2012, Hetrick and colleagues added a Spanish trial of 2005 (data only) not included before (23). In the systematic review, they considered two age ranges: (1) adolescents with an age range of 12 or 13 to 17 or 18 and (2) a mixed age group for “children and adolescents” with a lower age range of six to eight years. In their new update, Hetrick et al did not change their conclusions and stated that “…with these limitations, it is difficult to answer questions about the effectiveness and safety of antidepressants for treating depression in children and adolescents”. They also highlight that health providers should “…provide accurate information to children and adolescents, and their families, about the uncertainties regarding the benefits and risks of newer generation
antidepressant medication as a treatment option for depression. If a decision to use medication is agreed then fluoxetine might be the medication of first choice given guideline recommendations and, if used, the risk of suicide should be assessed and monitored particularly closely”.

- Cox et al, 2012a (24) conducted a recent systematic review focusing on relapse prevention as an outcome and found only 9 trials. They report that the blinding and allocation concealment has been unclear. The authors communicate that they were unable to make a conclusion and called for more trials.

- Cox et al, 2012b (25). They included ten studies to compare psychological therapies alone and in combination for depression versus antidepressants, involving 1235 participants. Their participants were children and adolescents aged eight to 17 years in one trial and adolescents over the age of 11 in nine trials. They were unable to conclude about the effectiveness of individual treatments and preference of any treatment over the other and asked for additional trials.

Overall, it seems that few trials have involved young children in their studies (26). According to our reviews, no additional evidence of a different direction has emerged since our previous evidence review on the effectiveness of SSRIs including fluoxetine for children under 12.

11. Summary of comparative evidence on safety:

11.1. Estimate of total patient exposure to date

Fluoxetine is the first new generation antidepressant. Millions of people with depression and some other mental disorders have received it since 1974. Only in UK nearly 6 million prescriptions included fluoxetine in 2011(27). Over time children with depression were also started on this medication. We do not have statistics on the number of children and adolescents who have used it but it should be considerably high too. Even since 2004, despite a general decrease in the use of antidepressants in younger people in US (28), it seems that it has been the the only medicine certified for use in this age group in many countries (3,20).

11.2. Description of adverse effects/reactions

From WHO Model formulary for children, 2010(26)

**Clinical worsening of depression or suicidal ideation may occur.**

**Adverse effects:**

**Common:**

Nausea, agitation, insomnia, drowsiness, tremor, dry mouth, diarrhoea, dizziness, headache, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, rhinitis, myalgia, rash, chills, euphoria, yawning.

**Uncommon:**

Extrapyramidal reactions (including tardive dyskinesia and dystonia), sedation, confusion, palpitations, tachycardia, hypotension, hyponatraemia (as part of syndrome of inappropriate antidiuretic hormone secretion), abnormal platelet aggregation/haemorrhagic complications (e.g. bruising, epistaxis, gastrointestinal and vaginal bleeding), alopecia, changes in blood sugar, serotonin syndrome.

**Rare:**

Elevated liver enzymes, hepatitis, hepatic failure, galactorrhoea, blood dyscrasias, seizures, akathisia, paraesthesia, taste disturbance, toxic epidermal necrolysis and neuroleptic malignant syndrome.

11.3. **Identification of variation in safety due to health systems and patient factors**

11.4. **Summary of comparative safety against comparators**

In mhGAP review of 2009 the data on the relative risk of suicidal behavior attributed to fluoxetine was judged to be difficult to interpret because of wide confidence intervals, although the related adverse events and suicide behaviour/ideation was higher in fluoxetine than placebo-related patients. However, fluoxetine was shown to be less likely than placebo to lead to discontinuation of treatment for any reason. Hyperkinesias, headache and skin rash were more common in fluoxetine than with placebo.

- Williams SB et al 2009(21). See the limitations mentioned under 10.

- Hetrick SE et al, 2012, see under 10. They reported “… an increased risk (64%) of suicide-related outcomes for those on antidepressants compared with those given placebo”. Rates of adverse events was higher for those receiving antidepressant. There was no evidence that one particular type of newer generation antidepressant had a larger effect than the others when compared to placebo.”(22). The additional trial that they added in their recent update (23) did not address adverse events.

- Cox et al, 2012 a, see 10.(24) The majority of trials that involved antidepressant medication reported adverse events including suicide-related behaviours. However, there were not enough data to show which treatment approach results in the most favourable adverse event profile.
- Cox et al, 2012 b (25), see 10. They focused on suicide related adverse events but were not able to combine the different studies as this outcome was not reported in the same way in different trials. Suicidal ideation was found measurable in one study and was significantly higher in the antidepressant medication group compared with the psychological therapy Group.

Overall, systematic reviews since mhGAP review of 2009 have not offered a different safety profile for fluoxetine for children below age of 12. This has also been highlighted in the past by some other groups of reviewers indicating that to conclude for recommending fluoxetine for younger children we still need additional studies (29,30).

Though psychotherapy is at least in the short term effective for youth with depression in general, again it has been shown to be more effective in adolescents than children (11). After the March 2004 Food and Drug Administration (FDA) warning on antidepressant suicidality indicating the possible risk of increased suicidal behaviour and ideas in children and adolescents which excluded fluoxetine, an overall decrease in antidepressant treatment for youth was reported and psychotherapy without medication increased (28).

In developing countries mental health care to children is predominantly delivered through primary care or by general psychiatrists (not specialized in children) and pediatricians (31). According to a WHO survey in EMRO, in 67% of the countries the majority of service is provided by general psychiatrists, paediatricians and primary care physicians or non-physician primary health care workers. A considerable proportion of them may not have the skills and the time to communicate with the child, parents and school or to consider alternative treatments before reverting to medicines (32).

Currently fluoxetine is a complementary medicine for children >8 years in WHO essential list of medicines for children. It seems that moving this age to > 12 years would be a more prudent risk-benefit decision.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

Psychotherapy is somewhat more costly than pharmacotherapy for UK inpatients care (33). However, the situation is different in low and middle income countries, where staff costs are much lower. Structured psychological interventions delivered through community and primary care providers have been shown to be effective and low cost (34,35,36,37) and have been recommended in mhGAP.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Not applicable

Not applicable

15. Proposed (new/adapted) text for the WHO Model Formulary

No adaptation needs to be made to the adult formulary if the decision is taken to move it to the adult list, except the following:

**Clinical worsening of depression or suicidal ideation may occur especially in adolescents and young adults up to 24.**

Depression and certain other mental disorders are themselves associated with increased risk of suicide.

**Special Notes: WHO age restriction: > 12 years.**

*Acknowledgement: I appreciate comments from Drs M. Van Ommeren, C. Servili and S. Saxena.*

**References:**


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

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

- 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


EXCLUDED FROM GRADE TABLES


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


### PICO table

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<tr>
<th>Serial no.</th>
<th>Intervention/Comparison</th>
<th>Outcomes</th>
<th>Systematic reviews used for GRADE</th>
<th>Explanation</th>
</tr>
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<td>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</td>
<td>Hazell et al, 2002 (update 2008) No data No data No data No data No data No data</td>
<td>Hazell et al, 2002 (update 2008) is a recently updated Cochrane Review</td>
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Hetrick et al (2007) is a recently published Cochrane Review
**Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder**

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<th>User and family satisfaction</th>
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### 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:


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lack of response

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<th>Other considerations</th>
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<th>Absolute</th>
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depressive symptoms (Better indicated by lower values)

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overall functioning (Better indicated by lower values)

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adverse effects

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user and family satisfaction (Better indicated by lower values)

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

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:

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

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<tr>
<td>-</td>
<td>MD 0 higher (0 to 0 higher)</td>
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</table>

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.

Table 3

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-05-25
Question: Should fluoxetine vs. placebo be used for children with depression?
Settings:
**Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder**

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<tr>
<th>depressive symptoms (Better indicated by lower values)</th>
<th>randomized trials</th>
<th>very serious inconsistency</th>
<th>no serious indirectness</th>
<th>no serious imprecision</th>
<th>None</th>
<th>0&lt;sup&gt;a&lt;/sup&gt;</th>
<th>0&lt;sup&gt;b&lt;/sup&gt;</th>
<th>-</th>
<th>MD 6.72 lower (10.55 to 2.88 lower)</th>
<th>LOW</th>
<th>CRITICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>overall functioning (Better indicated by lower values)</td>
<td>randomized trials</td>
<td>very serious&lt;sup&gt;2&lt;/sup&gt; inconsistency</td>
<td>serious&lt;sup&gt;2&lt;/sup&gt; indirectness</td>
<td>serious&lt;sup&gt;3&lt;/sup&gt; imprecision</td>
<td>None</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>MD 3.76 higher (3.19 lower to 10.71 higher)</td>
<td>VERY LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>adverse effects</td>
<td>no evidence available</td>
<td>0/0 (0%)</td>
<td>RR 0 (0 to 0)</td>
<td>0 fewer per 1000 (from 0 fewer to 0 fewer)</td>
<td>CRITICAL</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>user and family satisfaction (Better indicated by lower values)</td>
<td>no evidence available</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>MD 0 higher (0 to 0 higher)</td>
<td>IMPORTANT</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

2. Only one study contributed to the analysis.
3. Less than 100 patients are included in the analysis.
5. One study has a dropout rate exceeding 30%.
6. Not reported.
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:
## Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

### Quality assessment

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>paroxetine</th>
<th>placebo</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious²</td>
<td>serious³</td>
<td>none</td>
<td>22/49 (44.9%)</td>
<td>22/47 (46.8%)</td>
<td>RR 0.96 (0.62 to 1.48)</td>
<td>19 fewer per 1000 (from 178 fewer to 225 more)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Depressive symptoms (Better indicated by lower values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious²</td>
<td>serious³</td>
<td>none</td>
<td>0⁶</td>
<td>0⁶</td>
<td>-</td>
<td>MD 5.27 higher (0.00 to 10.54 higher)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Overall functioning (Better indicated by lower values)</strong></td>
<td></td>
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<tr>
<td>0</td>
<td>no evidence available</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious²</td>
<td>serious³</td>
<td>none</td>
<td>34/49 (69.4%)</td>
<td>30/47 (63.8%)</td>
<td>RR 1.09 (0.82 to 1.44)</td>
<td>57 more per 1000 (from 115 fewer to 281 more)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>User and family satisfaction (Better indicated by lower values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>0</td>
<td>no evidence available</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

2 Only one study contributed to the analysis.
3 Estimate ranges from appreciable benefit to appreciable harm.
5 Estimate ranges from appreciable harm to no difference.
6 Not reported.
Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

Table 5

Author(s): Corrado Barbui, Taghi Yasamy
Date: 2009-05-25
Question: Should sertraline vs. placebo be used for children with depression?
Settings:

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>Effect</td>
</tr>
<tr>
<td></td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>Quality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
<td>no evidence available</td>
<td>None</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>depressive symptoms (Better indicated by lower values)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2 randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious (^1)</td>
<td>0(^1)</td>
<td>0(^4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>overall functioning (Better indicated by lower values)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no evidence available</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>MD 0 higher (0 to 0 higher)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>adverse effects</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no evidence available</td>
<td>None</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>Not estimable</td>
<td>0 fewer per 1000 (from 0 fewer to 0 fewer)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>user and family satisfaction (Better indicated by lower values)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no evidence available</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>MD 0 higher (0 to 0 higher)</td>
</tr>
</tbody>
</table>
### Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

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:**  

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td></td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Suicide ideas / behaviour (children and adolescents, 6-18 years)</td>
<td></td>
</tr>
<tr>
<td>9th</td>
<td>randomized trials</td>
</tr>
</tbody>
</table>

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

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


13
Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder


**From evidence to recommendations**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narrative summary of the evidence base</strong></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>For fluoxetine, in terms of responders and in terms of score on a depression measure, there is limited evidence suggesting a significant beneficial effect.</td>
</tr>
<tr>
<td></td>
<td>In terms of treatment acceptability and adverse effects, the evidence is sparse and inconclusive.</td>
</tr>
<tr>
<td></td>
<td>In terms of suicide ideas/behaviour, for the group of selective serotonin reuptake inhibitors, including children and adolescents together, there is</td>
</tr>
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</tr>
</tbody>
</table>
Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

<table>
<thead>
<tr>
<th>Summary of the quality of evidence</th>
<th>The quality of the evidence was LOW or VERY LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance of benefits versus harms</td>
<td>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.</td>
</tr>
<tr>
<td>Values and preferences including any variability and human rights issues</td>
<td>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.</td>
</tr>
<tr>
<td>Costs and resource use and any other relevant feasibility issues</td>
<td>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</td>
</tr>
</tbody>
</table>
Antidepressants (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors) in children 6-12 years of age with depressive episode/disorder

| 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