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When do you Prescribe Antidepressants to Depressed Children?

Cesar Soutullo · Ana Figueroa-Quintana

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Abstract Major depressive disorder (MDD) in children and adolescents is a public health problem that requires evidence-based management. Our objective is to review available studies, with a PubMed search, and briefly summarize safety and efficacy results of (mostly SSRI) antidepressants in children and adolescents with MDD. Fluoxetine and escitalopram are safe and effective in the treatment of MDD in children and adolescents both in reduction of symptoms, and in remission/response rates. However, response rates are lower than for non-OCD anxiety. Sertraline also had positive results in one study that pooled results from two studies. The number needed to treat (NNT) for MDD is 10, and the number needed to harm (NNH) for suicidality is 112. Methodological limitations in the studies include, mainly, high placebo response rates, associated with multiple study sites, younger patients, and lower MDD severity. Treatment should be maintained close to 1 year after remission, to prevent relapse. FDA-approved fluoxetine and escitalopram are safe and effective in the treatment of pediatric MDD. Sertraline also has some data supporting its efficacy and safety, but is not FDA-approved. The possible modest increase in suicidal ideation in some patients should be known by clinicians, but the risk/benefit ratio is 1 to 11.2 times favorable to using SSRIs in moderate to severe MDD.

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C. Soutullo (✉)
Director, Child & Adolescent Psychiatry Unit,
University of Navarra Clinic, Avenida Pio XII, 36,
31008 Pamplona, Spain
e-mail: csoutullo@unav.es

A. Figueroa-Quintana
Director, Child & Adolescent Psychiatry Unit, Perpetuo Socorro Hospital, Las Palmas de Gran Canaria, Spain

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Introduction

The prevalence of major depressive disorder (MDD) is 2.8 % in children younger than age 13, and 5.6 % in adolescents (13–18 years old) [1], with a point prevalence of adolescent MDD up to 4–6 % [2]. We have known for many years now that about 60 % of adolescents with MDD will have a recurrence in adulthood, and that adults with a history of adolescent MDD have higher rates of suicide than those without such history [3]. Therefore, MDD is a major public health problem, a frequent, serious and treatable disorder, and a potentially preventable cause of disability, academic failure, substance abuse, early pregnancy, and mortality in children and adolescents [4–6, 7••].

The diagnostic criteria for MDD are virtually the same for children and adults (except irritable mood, accepted in children and adolescents in addition to depressed mood and anhedonia as an A criteria) [8]. However, the clinical presentation may differ from adults. Children are more likely to have somatic symptoms, restlessness, separation anxiety, phobias, and hallucinations. Adolescents with depression are more likely to experience anhedonia, boredom, hopelessness, hypersomnia, weight change (including failure to reach appropriate weight milestones), alcohol or drug use, and suicide attempts [9].

Antidepressants are efficacious for pediatric MDD, OCD and other anxiety disorders, although effects are strongest in non-OCT anxiety disorders, intermediate in OCD and more modest in MDD [10]. Only Fluoxetine is approved for acute and maintenance treatment of MDD in children (8–17 years old), and escitalopram for adolescents (12–17 years old) [11••]. There are also two positive studies of sertraline in children 6–17.

However, there are some negative studies of citalopram (N=1), escitalopram (N=1), paroxetine (N=3), and the non-SSRI mirtazapine (N=2), nefazadone (N=2), and venlafaxine (N=2). These studies had similar response rates to those found in positive studies, but much higher placebo effect. High placebo response rates were associated with mild depression (versus marked or severe) in the probands, high number of study sites, and younger age of the patients (children vs. adolescents) [12]. There are also reports of SSRI treatment-emergent adverse events, including the onset of suicidal ideation (but no reported completed suicide) in children and adolescents treated with SSRI for MDD, but not in those treated with SSRI for anxiety disorders [7••, 10, 13].

The objective of this paper is to review and briefly summarize the efficacy, tolerability and safety in available double-blind placebo controlled randomized studies of antidepressants in MDD in children and adolescents. Our goal would be to assist clinicians in their risk/benefit discussion with parents prior to their informed consent decision to select the best evidence-based available treatment for their child with MDD. This informed consent decision by the parents has to be based in factors such as: severity of MDD (moderate or severe), history of a prior MDD episode or prior SSRI treatment, family history of unipolar MDD versus bipolar disorder and family history of good response to and SSRI, environmental stressors (with special interest in bulling) that have been removed with no improvement in mood, and evidence of a good CBT trial with lack of response [14].

Method

We conducted a literature search (PubMed) on the recent published studies on antidepressant use in children and adolescents: keywords: antidepressants and children and adolescents. We also did manual search on the references of those papers. We limited the search to randomized double-blind placebo controlled trials of SSRIs and other antidepressants, and we also included recent review papers and meta-analysis that also include unpublished studies. We organized this review in a very straight forward way, trying to answer five questions:

1) Are antidepressants effective in children and adolescents with MDD (more effective than placebo)?,
2) What antidepressants should be used first?,
3) How long should we use an antidepressant after an initial response?,
4) What should we do if there is no response to one antidepressant?, and
5) Are antidepressants safe in children and adolescents with MDD?

Results

Are Antidepressants Effective in Children and Adolescents with MDD?

There are at least 19 studies that evaluated the efficacy of antidepressants compared to placebo [7••], 15 with SSRI, and four with non-SSRI new-generation antidepressants in a total of 3,335 children or adolescents (Table 1).

Studies with SSRI Antidepressants

We found 15 studies that used the SSRI class: trials of fluoxetine (N=5) [15–19], escitalopram (N=2) [20, 21], sertraline (N=2) [22], citalopram (N=2) [23, 24], and paroxetine (N=4) [25–28].

Studies with Venlafaxine

In the selective norepinephrine reuptake inhibitor (SNRI) class there were two trials of venlafaxine published together [29],

Studies with Mirtazapine

and in the tetracyclic antidepressant (TeCA) class there were two trials of mirtazapine [30].

The Treatment for Adolescents with Depression Study (TADS) [18] was the first trial that directly compared the effectiveness of fluoxetine, CBT, their combination, or placebo in adolescents with MDD [18, 31]. After 3 months of treatment, fluoxetine was found to be superior to placebo (response rate of 61 % vs. 35 %), but CBT (43 %) was not different from placebo. However, only the combination use of fluoxetine and CBT induced remission rates higher than placebo (37 % vs. 17 %) [32]. The analyses of the subsequent 6 months of treatment found that there was a gradual convergence of treatment effects across the three active treatment groups so that, at the 9-month assessment, fluoxetine, CBT, and their combination did not differ in response rate (fluoxetine: 81 %, CBT: 81 %, combination 86 %) or remission rate (Fluoxetine 55 %, CBT 64 %, and combination 60 %) [31, 33].

However, the combination of SSRI treatment with CBT was superior to treatment with SSRI alone in some [18], but not all acute MDD studies [34–36].

In 2007 a meta-analysis by Bridge et al. [10] found that based on data from 13 trials (N=2,910) available then, pooled absolute rates of response were 61 % (95 % CI, 58 % to 63 %) in participants treated with antidepressants and 50 % (95 % CI, 47 % to 53 %) in those treated with placebo, yielding a pooled risk difference of 11 % (95 % CI, 7 % to 15 %), and NNT of 10 (95 % CI, 7 to 15), with a

Table 1 Controlled pediatric MDD studies

	Medication	Reference	Ages	Number of studies
Positive studies*	Fluoxetine	Emslie et al. [16], Emslie et al. [17], TADS [19], Almeida-Montes & Friederichsen [15]	6–17	4
	Escitalopram	Emslie et al. [20]	12–17	1
	Sertraline	Wagner et al. [22] **	6–17	1 (a priori pooled analysis, individual trials negative)
Negative studies	Escitalopram	Wagner et al. [21]	6–17	1
	Citalopram	von Knorring et al. [23]	13–18	1
	Paroxetine	Keller et al. [25], Emslie et al. [27], Berard et al. [26], Paroxetine Trial 1 [28]	7–17	4
	Venlafaxine	Emslie et al. [29]**	7–17	2
	Mirtazapine	Mirtazapine Trials 1 & 2 [30]**	7–17	2

*On primary outcome measure

**References 22, 29 and 30 include two trials in one paper

NNT for fluoxetine of 6. Pooled absolute rates of suicidal ideation/suicide attempt were 3 % in antidepressant-treated participants versus 2 % in those receiving placebo. The pooled risk difference was 1 %, so the NNH was 112 [10]. In this comprehensive meta-analysis, NNT for SSRI´s in 6 OCD trials (N=705) was 6 (95 % CI, 4 to 8), and NNH for suicidal ideation/suicide attempt in OCD anxiety trials was 200. And NNT for SSRI´s in 6 non-OCD anxiety disorder trials (N=1,136) was 3 (95 % CI, 2 to 5), and NNH for suicidal ideation/suicide attempt in these trials was 143. Thus the efficacy of antidepressants seems to be higher in non-OCD anxiety, intermediate in OCD, and lower in MDD, and risk for suicidal ideation/suicidal attempt higher in MDD than in anxiety trials [10], but still with a favorable risk/benefit ratio on 10 to 112.

What Antidepressant Should we Use?

The two only FDA-approved medications for the treatment of MDD in pediatric ages are: fluoxetine (for children and adolescents ages 7–17), and escitalopram (adolescents 12–17). There are also other positive studies that support the use of citalopram (1 study in patients 7–17 years old) and sertraline (2 studies in patients 7–17 years old), but they are not FDA-approved. Based on available studies, fluoxetine in children and adolescents (6–17) (response rates 52–61 % vs. placebo: 33–37 %) [15–19], and escitalopram in adolescents (12–17) (response rates 64 % vs. placebo: 53 %) [20, 21] have evidence of efficacy in the treatment of major depression. Additionally, there is evidence that sertraline (response rate 63 % versus placebo 53 %) could be beneficial in children ages 6 to 17 [22], and there was also one positive study with citalopram (response rates 45 % vs. placebo 45 %) [24]. The negative studies had similar response rates to the positive studies (49–69 %), but the placebo response was higher than in the positive studies (41–61 %), thus the medication did not separate from placebo. Factors associated with high placebo response rates included: younger age of the patient, lower baseline severity of depressive symptoms, and higher number of sites in the study. Predictors of better response to CBT+Medication were: more comorbidity, no abuse history, and lower hopelessness. Predictors of suicidal adverse events were: high baseline suicidal ideation, family conflict, and drug or alcohol abuse [12].

How Long Should we Treat a MDD Episode?

To try to answer this question, Cheung et al. [37] developed a study on 93 adolescents with MDD, who received a 12 week (3 month) open-label sertraline course, those who responded (N=51, 54.8 %), continued on open-label sertraline for another 24 weeks (6 months). At the end of this 36 week (9 month) period, those who maintained the response (N=22; 23.6 % of the original sample) were randomized either to continue on sertraline (N=13) or to change to placebo (N=9), for another 52 weeks (1 year). After 52 weeks of double blind continuation 38 % of those on sertraline remained on response, but 0 % of the patients on placebo maintained the response [37]. Thus, 6 months after achieving a response, a randomization into placebo resulted in a relapse. Although the sample size was small, the findings suggest a possible benefit of maintenance treatment with sertraline over placebo. Larger studies are needed, because survival analyses found no significant differences between the groups (p=0.17) [37].

Continuation treatment after a good response is achieved is important to increase the likelihood of sustained remission, and to prevent relapse. If 6 months is too short for continuation, how long is enough? There is no clear empiric

answer to his question, other than expert guidelines that recommend treatment up to 6–12 months after achieving full remission, and a gradual discontinuation afterward during a period that is free of major stressors (not during the beginning or the end of school year, nor during final exams) [38]. In view of the results of the study by Cheung et al. [37] a duration of treatment closer to 12 months after full remission is probably more likely to prevent relapses. Another important decision is when during the year to stop the treatment. Controlling for baseline differences in the Treatment of SSRI resistant depression in adolescents study (TORDIA) [39], adolescents ending their 12-week treatment during summer vacation had odds 1.7 times (95 % confidence interval = 1.02-2.8, p=0.04) greater to have an adequate response than those ending their treatment while being in school [11••, 40]

In another interesting study by Kennard et al. [41], 66 adolescents ages 11–17 with MDD, were assigned to an open-label course of fluoxetine for 12 weeks. Those who responded were randomly assigned to continue on fluoxetine (N=24), or continue on fluoxetine+CBT (N=22). After 6 months of treatment with either arm, the rates of relapse were: 37 % with fluoxetine, and 15 % with fluoxetine+CBT. Thus, similar to results from the TADS [18, 31], adding CBT would reduce the rate of relapse compared with medication alone [41].

What do we do if the Patient Does not Respond to an (Adequate Dose & Duration) SSRI Trial?

There is some available evidence of how to proceed once the patient does not respond to an adequate dose and duration (8 weeks) of an SSRI from the TORDIA study [39].

- Treatment of SSRI resistant depression in adolescents (TORDIA). Adolescents (N=334; ages 12–18) with clinically significant depression (Children Depression Rating Scale $\geq$ 40 and CGI-Severity $\geq$ 4 [moderate to severe]) who had not responded to an adequate 8 week course of an SSRI were eligible to participate in the study and were randomized to one of four treatments:

  1) switch to a different SSRI (citalopram or fluoxetine),
  2) switch to venlafaxine,
  3) switch to SSRI+CBT, or
  4) switch to velanfaxine+CBT.

This study was done in the middle of the suicidality controversy and had difficulties recruiting, but it was finished [42•]. The acute phase was 12 weeks, responders could remain in their treatment arm, and non-responders received open treatment for an additional 12 weeks. The results showed: 1) A response rate of 50 % to an alternate treatment, 2) similar response to another SSRI (47 %) or to venlafaxine (48 %), but venlafaxine was associated with more side-effects. 3) The combination of CBT+antidepressant had a better response rate (55 %), than the antidepressant alone (41 %).

Thus the evidence-based recommendation for an adolescent with moderate to severe depression who does not respond to 8 weeks of an SSRI is to change to another SSRI (fluoxetine or citalopram), and add CBT. That would achieve a response in 55 % of patients [40]. Predictors of response included: less severe depression, less family conflict, and absence of (non-suicidal) self-injurious behavior [43].

Are Antidepressants Safe in Children and Adolescents?

SSRI antidepressants are usually well tolerated in children and adolescents, but the long term effects of these agents are not known. The adverse events of the SSRIs and other novel antidepressants appear to be similar, dose-dependent, and may subside with time [38]. The most common adverse events include: gastrointestinal symptoms, sleep changes (insomnia, somnolence, vivid dreams, nightmares, impaired sleep), restlessness, diaphoresis, headaches, akathisia, appetite and weight changes (increase or decrease), and sexual dysfunction. Venlafaxine can mildly increase blood pressure, and about 3–8 % of youth treated with Venlafaxine or SSIRs, particularly children, may also show increased impulsivity, agitation, irritability, “silliness”, and “behavioral activation” [11••, 38]. Some side effects are more frequent at the beginning of treatment, thus it is recommended to start with a low dose for a few days, then increase to the initial therapeutic dose, and wait for 4 weeks until considering the next dose increase. Increasing the dose faster will not accelerate response, but will increase the risk of adverse events [11••].

One potential adverse event that has raised clinician, family and media attention is the issue of suicidality. Historically, antidepressants have been reported to be associated with a small increase in suicidal ideation since as early as 1950; initially with tricyclics, then with SSRI´s in adults in the 1980s and early 1990s [44], followed by case reports of children during the 1990s [45]. An initial review of 24 studies (16 on MDD) found that the use of andidepressants in pediatric patients was associated with a modestly increased risk for suicidality, defined as suicidal ideation or attempt, but there was no completed suicide in the trials. The overall relative risk for suicidality for all the trials and indications (depression, anxiety and OCD) was 1.95 (95 % CI, 1.28–2.98), and for SSRIs in MDD trials 1.66 (95 % CI 1.02–2.68) [13]. Of note, in all of these 24 studies, the 95 % confidence interval included the value 1, thus, there is a

95 % chance that the risk of increased suicidality is 1 (equal to placebo). Another limitation of this paper is that the results are not based on prospectively designed outcomes of the trials designs [46, 47].

In a more recent review of 27 studies, authors found a 3 % rate of suicide ideation or attempts (not completed suicide) in patients on antidepressants (95 % CI, 2 %–4 %), versus 2 % (95 % CI, 1 %–2 %) in the placebo group for depression, anxiety and OCD. Risk difference was 1 % (95 % CI, −0.1 % - 2 %), not statistically significant (p=0.08) [10]. Neither of the meta-analysis found any cases of completed suicide.

Due to reports of this possible modest increased risk of suicidality, the British UK Medicines and Healthcare Products Regulatory Agency (MHRA) warned UK physicians against pediatric use of sertraline, citalopram and escitalopram due to "unfavorable risk-benefit profile" [48]. On October 2004, the U.S. FDA issued a "Black Box Warning" on all antidepressants to inform of an increased risk of suicidality in children and adolescents [49], in 2007 in patients up to 24 years old, and also similar warnings appeared in other countries. The goal of the warning was to make clinicians and families aware of this low frequency potential risk and balance risk/benefit ratio and stimulate informed-consent decision making, but not to forbid the use of antidepressants up to age 24.

Between 1999 and 2003, before the U.S. FDA Black Box Warning, there was an increase in the rate of diagnosis of MDD [50] and in the use of SSRIs in all ages [51, 52]; e.g., from 2002 to 2003 pediatric use of all antidepressant significantly increased at a rate of 36 % [53]. In parallel, there was a 35.7 % decrease in the rates of suicide [54].

After the FDA black box warning was issued, there was a decrease in the rate on diagnosis of MDD in children and adolescents [50], and also a 22 % decrease in SSRI-prescription for youths in the United States, in the Netherlands [51, 55] and in other countries. During this period there was an increase in the rate of completed suicide of 14 % in the USA (2003-2004) [51], 49 % in the Netherlands (2003-2005) [51] and 25 % in Canada (2003-2005) [52]. This association in time does not imply causality, however, if SSRI was increasing suicidality, a decrease in SSRI use should have been followed by a decrease in suicide rates, not an increase. However, other studies suggest that after the black box warning, there was a statistically non-significant decline in antidepressant treatment of youth, including a significant deceleration in the rate of treatment with SSRIs other than paroxetine, but that the absolute rate of overall antidepressant treatment of youth did not significantly decrease [53].

Because the TADS excluded patients with high suicide risk [18, 31], the NIMH funded the Treatment of Adolescent Suicide Attempters (TASA) study [56]. This was an open trial that included 124 adolescents with unipolar MDD who had made a recent suicide attempt. The majority received specific psychotherapy and medication, and were followed up 6 months. The morbid risks of suicidal events and attempts were 0.19 and 0.12, respectively, lower than in other comparable samples, suggesting that intervention is helpful [56].

In summary, suicidal ideas and attempts are quite prevalent in the general pediatric population; 2.6 %–16 %, and 0.5-5 % respectively [57], and suicidality is a common symptom in major depression [58]. Some studies suggest that there is an association between SSRI treatment in pediatric patients with MDD and a modest increase in suicide ideation and attempts (but not completed suicide) [13, 18, 59–61]. Other studies suggest that there is no evidence of this association [54, 55, 62] and that SSRIs reduce suicidal ideation and attempts [36, 63, 64••]. Studies show that the vast majority of suicide victims (completed suicide) were not on antidepressants at the time of death, and even those to whom they had been prescribed had no antidepressant blood levels on toxicology [65]. This suggests low compliance, and such perhaps why they were not better.

Bridge et al. [10] found that the NNT for children and adolescents with MDD is 10, and the NNH (to present suicide ideas or attempts) is 112, which suggests the risk/benefit ratio is favorable to the use of antidepressants in children with moderate or severe depression. Moreover, with this data, if because of a potential increase in suicidality, clinicians stop prescribing SSRIs to children and adolescents with depression, for each patient who we could prevent having suicidal ideation or attempts, 11 would not achieve remission. Treatment with SSRI should always be combined with CBT when available, as it decreases the suicidality risk [18].

According to one study an increase in SSRI sales of 1 pill per capita (12 % of the year 2000 sales levels) reduces suicide by 5 %, implying that each additional $22,000 spent on SSRIs will avert one suicide completion [66].

Conclusions

FDA-approved fluoxetine and escitalopram are safe and effective in the treatment of pediatric MDD. Sertraline and citalopram also have some data supporting its efficacy and safety, but are not FDA-approved. The possible modest increase in suicidal ideation in some patients should be known by clinicians. The NNT for children and adolescents with MDD is 10, and the NNH (to present suicide ideas or attempts) is 112,

suggesting the risk/benefit ratio is favorable to the use of antidepressants in children with moderate or severe depression [10]. No completed suicide was found in any of the 19 randomized double blind placebo controlled trials.

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Ana Figueroa-Quintana has served on speakers bureaus for Shire and Janssen, and received royalties from Editorial Médica Panamericana.

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