Special Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2007;76:5–14
DOI: 10.1159/000096360

Should the Use of Selective Serotonin Reuptake Inhibitors in Child and Adolescent Depression Be Banned?

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Key Words
Youth depression · Serotonin reuptake inhibitor ban · Suicidal behavior

Abstract
Background: European and US pharmaceutical agencies have recently warned against the use of selective serotonin reuptake inhibitors (SSRIs) in child and adolescent depression. This came as a surprise to many practitioners, who had made treatment decisions based on data from pharmaceutical trials using adult samples. ***Method:*** The author reviews the recent literature relevant to the use of SSRIs in youth depression, including psychiatric clinical trials, pharmacology and drug safety data. Recommendations and rationales for the use of SSRIs in this context are offered. ***Results:*** Ten publications, comprising a total of 2,046 patients, evaluated the efficacy of four SSRIs (fluoxetine, paroxetine, sertraline and citalopram) in child and adolescent depression. It is noted that an additional 6 trials (with a total of 1,234 patients) were not reported by the industry because of a lack of efficacy or problematic side effects, including suicidal behaviors. Meta-analyses revealed no data supporting the use of SSRIs, except for fluoxetine. To formulate recommendations for clinical practice, it is necessary to examine specific issues such as (1) the link between SSRIs, depression and suicidal risk; (2) SSRI age-related specific effects, and (3) the high placebo response in child and adolescent depression. ***Conclusion:*** An SSRI prescription is still a second-line option in severe and resistant forms of youth depression. However, in children and adolescents only specialists well trained in child and adolescent psychiatry should prescribe SSRIs.

Introduction

Child and adolescent depression has been a public health concern for some time because of its implication in suicidal acts and youth morbidity [1, 2]. During the 1980s, the arrival of the selective serotonin reuptake inhibitors (SSRIs), which resulted in far less side effects than tricyclics (TCAs) or monoamine oxidase inhibitors, was viewed as an important step in the treatment of affective disorders, first in adults and then in children and adolescents. In the early 1990s, SSRI use in children and adolescents increased rapidly in developed countries, sometimes at a higher proportion than the prevalence rate of depression in this age range [3]. Warnings against the excessive use SSRIs are fairly recent and have led to a first decision in April 2003 by the United Kingdom Committee on Safety of Medicines, who banned paroxetine use for depression in adolescents and children [4]. In December 2003, the committee expanded the prohibition to

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include all SSRIs, except for fluoxetine. In June 2003 and later in December of the same year, the United States Food and Drug Administration issued a 'black box' warning against the risk of suicidal behavior associated with the use of SSRIs and other antidepressants in child and adolescent depression [5]. Finally, a year later (in December 2004), the European Medicine Agency agreed with the UK committee [6]. These decisions came as a surprise to clinicians as well as to patients and their families. In fact most practitioners had been relying on data from pharmaceutical trials using adult samples in their practice with children and adolescents, and most of them did not have specific information on the treatment of depression in young people.

In this context, the present report (a) summarizes literature data concerning the treatment of child and adolescent depression with SSRIs; (b) describes the reasons that led to agencies' recommendations, and (c) discusses how to integrate these recommendations into our clinical practice by examining other studies on treatment and follow-up in child and adolescent depression. I argue that rules should not be applied blindly, and I consider that limiting review to only randomized pharmaceutical trials versus a placebo does not allow a deep reflection. In fact, we are reaching the limits (1) of the 'evidence-based medicine' concept, a scientific groundwork derived from the work of these agencies and (2) of the rhetoric of scientific debates that always includes some of the elements of propaganda, namely filtering information, engineering opinion, using the public relations industry and marginalizing dissident cultures [7]. The first-line treatment of child and adolescent depression is psychotherapy [8]. Nevertheless, psychotherapy is not appropriate in many clinical situations (e.g., adolescent refusal, psychotic depression, stuporous catatonia). In severe cases, other therapeutic approaches have been recommended: hospitalization, milieu therapy or residential treatment [9–11], antidepressant drugs [1], and electro-convulsive therapy [12, 13].

Review of Published Controlled Randomized Trials of SSRIs in Child and Adolescent Depression

Table 1 summarizes all the published controlled randomized trials of SSRIs in child and adolescent depression. Overall, ten pharmalogical trials were published up to 2004, with a total of 2,046 children and adolescents [14–23]; half of these trials tested fluoxetine. Its usefulness has been demonstrated in the treatment of major depression in children and adolescents in three different double-blind placebo-controlled studies [15–16, 19] and the FDA has recently recommended its use in these circumstances. Nevertheless, the superiority of fluoxetine over placebo was modest because it was not seen within all efficacy variables and within all types of statistical analyses [24].

Of the other five studies, three concerned paroxetine even though one of them did not compare it to a placebo. One study suggested a possible superiority of paroxetine versus placebo but only in secondary variable comparisons [18]. Publications on sertraline [22] and citalopram [23] suggested a small superiority of these drugs over placebo but statistical analyses raised major issues (see below). Furthermore, data published in the literature by drug corporations were scarce since most of the negative trials have not been reported [8].

What Were the Reasons That Led Agencies to Issue Warnings?

(1) From an evidence-based medicine perspective, the first reason was the absence of undeniable proof that SSRIs are more effective in the treatment of child and adolescent depression than placebo. In fact, agencies that had access to unpublished pharmacological trials revealed why six double-blind trials versus placebo were not published (two with paroxetine, two with citalopram and two with venlafaxine): either companies were not able to demonstrate a superior efficacy of the drug tested compared with placebo or problematic side effects had arisen from the medication. Meta-analyses were published following the agencies' recommendations, which had made available data from non-published trials to some methodologists [25, 26]. These analyses did not find paroxetine, sertraline, citalopram and venlafaxine to be superior to placebo. Only fluoxetine showed positive efficacy results, with a distinct superiority compared to placebo. In total, six trials with hundreds (n = 1,234) of children and adolescents were not published by companies in the scientific literature.

(2) The second reason, according to the agencies, was the absence of independent investigators. For example, in studies of depression in children and adolescents, only the TADS study was not industry funded (table 1). It has been argued that this situation led to minor data manipulations in many publications or positively biased presentations, omitting some details on the number of remissions or side effects (e.g. suicidal acts) [25]. Perlis et al.

Table 1. Published controlled pharmacological trials of SSRIs in child and adolescent major depressive disorder

Authors, year	n (age) duration	Treatment (dose) sponsorship	Study design and measures	Responders[1] (end-point analysis) drug vs. PBO
Studies with fluoxetine				
Simeon et al. [21] 1990	30 (13–18) 7 weeks	fluoxetine (20–60 mg/day) vs. PBO industry funded	1 week PBO washout parallel **HDRS**, CGI, SCL-58	66 vs. 66% (NS)
Emslie et al. [16] 1997	96 (8–18) 8 weeks	fluoxetine (20 mg/day) vs. PBO industry funded	3 weeks washout parallel **CGI**, CDRS	ITT: 56 vs. 33% (p = 0.02) but per protocol 74 vs. 58% (NS)
Emslie et al. [15] 2002	219 (8–18) 8 weeks	fluoxetine (20 mg/day) vs. PBO industry funded	3 weeks washout parallel CGI, **CDRS**	ITT: 65 vs. 53% (NS) but CDRS-R score more improved on active drug (p < 0.01)
Emslie et al. [17] 2004	40 (6–17) 51 weeks	fluoxetine (20–60 mg/day) vs. PBO industry funded	relapse prevention parallel for 32 weeks **CDRS-R**	ITT until relapse: 180 vs. 71 days (p = 0.046)
TADS [19] March 2004	439 (12–17) 12 weeks	fluoxetine (10–40 mg/day) vs. CBT vs. Flu+CBT vs. PBO NIH funded	parallel **CDRS-R**, CGI-I	Flu+CBT > Flu > CBT > PBO
Studies with other SSRIs				
Milin et al. [20] 1999	286 (13–19) 12 weeks	paroxetine (20–40 mg/day) vs. PBO industry funded	parallel K-SADS-dep, **MADRS**	74 vs. 71% (NS)
Keller et al. [18] 2001	275 (13–17) 8 weeks	paroxetine (20–40 mg/day) vs. imipramine (200–300 mg/day) vs. PBO industry funded	1–2 weeks washout parallel **CGI**, HDRS, K-SADS-dep	ITT: 65.6 vs. 52.1% vs. 48.3% (p = 0.02)
Wagner et al. [22] 2003	366 (6–17) 10 weeks	sertraline (50–200 mg/day) vs. PBO industry funded	2 weeks washout parallel **CDRS-R**, CGI	ITT: 69 vs. 59% (p = 0.05)
Braconnier et al. [14] 2003	121 (12–20) 8 weeks	paroxetine (20–40 mg/day) vs. clomipramine (75–150 mg/day) industry funded	2 weeks washout parallel **MADRS**, CGI	ITT: 65.1 vs. 48.3% (NS)
Wagner et al. [23] 2004	174 (7–17) 8 weeks	citalopram (20–40 mg/day) vs. PBO industry funded	1 week PBO parallel **CDRS-R**, CGI	ITT: 36 vs. 24% (p = 0.05)

Age is in years. PBO = Placebo; CBT = cognitive behavior therapy; BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS = Children's Depression Rating Scale; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impression-Severity; MADRS = Montgomery-Åsberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; ITT = intention-to-treat analysis; K-SADS-dep = Schedule for Affective Disorder and Schizophrenia for Adolescents 9-item Depression Subscore; SCL-58 = 58-item Hopkins Symptom Checklist.

[1] Results are given according to the protocol primary outcome measure (in bold in the fourth column), with the exception of the Keller et al. study, in which the primary outcome measure (HDRS) did not show a significant difference between active drugs and placebo.

[27] recently reported that, among 162 randomized double-blind placebo-controlled trials published from 2001 to 2003 in four major psychiatric journals, those that reported conflicts of interest were 4.9 times more likely to report positive results; this association was significant only among the subset of pharmaceutical-industry-funded studies. An article by Wagner et al. [22] provides an example of this kind of publication: the authors claimed to demonstrate sertraline superiority versus placebo in child and adolescent depression by combining two different drug trials in an a priori statistical design. Regrouping these two isolated and unpublished negative trials led to an increase of statistical power and the 'revelation' of an extremely small effect of superior efficacy compared to placebo at week 10. Nevertheless, as Jureidini et al. [25] showed by re-analyzing the authors' data at 6 and 8 weeks,

no superior efficacy of sertraline was shown at these points during the treatment, making the overall claim of efficacy rather unconvincing.

(3) The third reason concerned methodological issues such as the very high response to treatment during placebo testing in child and adolescent depression. This makes it difficult to find significant differences between the efficacy of the drug compared to placebo, and means that any significant differences that are found may only reflect small effect sizes. This issue has driven authors to choose numerous scales in their study designs that increase the probability of type I errors (a false rejection of the null hypothesis) [24, 25]. On the other hand, in studies with large sample sizes, significant effects which are not type I errors may only reflect small differences (effect sizes) between groups. For example, the NIH-funded TADS study, which had a comprehensive design including four groups (fluoxetine, cognitive behavioral therapy (CBT), placebo and fluoxetine-CBT combination treatment) and a sample size of 400, showed minimal differences between groups [19]. In addition this study showed that the combination of the two treatments was superior in efficacy to any treatment taken alone (fluoxetine or CBT) or placebo. Finally, as well as effect size, other methodological problems include biased results, e.g. a high proportion of study withdrawals (17–46%), or exclusion of severe cases [25].

(4) The last but not the least reason was an increased risk of suicidal behavior and ideation (defined as any of the following: suicide, suicide tendency, non-accidental overdose and thoughts of self-harm [26]) in medicated patients compared with those on placebo. This observation was reported in all meta-analyses and for each drug [8, 25, 26]. Given the context of a high prescription rate, agencies considered that the risk was too high compared to the benefits of most drugs in this respect, except for fluoxetine.

Before further in-detail analysis of the issues, I should comment on the motivation of agencies. Firstly it should be noted that the risk of suicidal acts is always present at the beginning of any treatment since suicide is a symptom of clinical depression. Secondly, agencies see many ethical problems and I do share their concerns. Pharmaceutical companies have a powerful position and good reason not to publish trial results that might have a negative impact on drug image. However, failure to publish may deprive the scientific community of valuable information. Similarly, since pharmaceutical companies are the main source of funding of pharmaceutical research, there are almost no studies comparing two drugs. In drug information sheets for clinicians and patients, nothing is said about the high placebo response in child and adolescent depression, or the age-specific SSRI action. In particular, is there indirect evidence that SSRIs do have an antidepressant effect in young people (e.g. do they increase the rate of mood switch in young bipolar subjects)? Finally, issues regarding treatment of a child or an adolescent with a depression resistant to psychosocial and/or psychotherapeutic approaches are not discussed.

SSRI Antidepressants and Suicidal Risks in Children and Adolescents

Meta-analyses have shown an increase in suicidal ideation and behaviors under SSRI medication in child and adolescent depression. This increase has been quantified: in groups receiving active treatment, suicidal ideation and/or behaviors represent 2.7–7.7%, compared with 0.6–3.6% in groups on placebo [25, 26]. The FDA meta-analysis found there was a small but significant group effect with more suicidal ideation and/or behaviors in youths given antidepressants than in those given placebo (risk ratio = 1.78, 95% CI = 1.14–2.77) [8]. Of note, no deaths associated with the active compounds occurred in the trials. However, it should be borne in mind that there was no increase in suicidal acts in the general population during the same time period (the 1990s, a period marked by economic inflation and growing SSRI use). In fact there was a slight decrease in suicides in children and adolescents [28]. These statistics do not mean that this decrease was necessarily due to SSRI prescription and overconsummation. In fact, in the same period, most Western countries had created prevention campaigns and programs, which may have helped to decrease suicide rate in youths. Similarly, a study by Olfson et al. [29] showed an inverse relation between antidepressant use and suicide rate in boys and older adolescents living in impoverished regions. It is difficult to know whether this relation was due to an SSRI-specific effect; although the authors collected data on antidepressant use, they discovered that many variables were not controlled, such as illegal drug use and psychosocial intervention. Finally, Isacsson et al. [30] showed in a Swedish database of 14,857 suicides over a period of 9 years that there was no increase of completed suicide associated with SSRI use in adults, children or adolescents.

It should be noted that suicidal risk associated with SSRIs is not restricted to children and adolescents, but has been also found in adult trials comparing drugs to

placebo. A sizeable data synthesis performed by sociologist and psychiatrist David Healy [31, 32] showed this problematic increase in groups of adult patients treated with active drugs, with an odds ratio superior to 4 between the active compounds versus placebo. The significance of Healy's studies has already been fully debated, in particular in *Psychotherapy and Psychosomatics* [for details, see 6]. Most importantly, two recent studies allowed this issue to be examined in terms of timeline. In a parallel randomized trial, Jick et al. [33] compared four drugs (amitriptyline, fluoxetine, paroxetine and atotiepine) for treatment of adult major depression. The results showed an increase of suicidal risk in each group, albeit limited to the first 10 days of treatment. The authors had in fact shown an old finding, often quoted in pharmacology manuals (e.g. the *Vidal,* the French pharmacology reference book), concerning the risk of disinhibition and suicidal acts under antidepressants at the first stage of treatment, which makes early prevention and monitoring essential. The second study used population-based data and showed that the risk of suicide death and serious suicide attempt in relation to initiation of antidepressant treatment was 1/3,000 and 1/1,000 treatment episodes, respectively [34]. Subsequent analyses showed: (1) stable suicide rates during the first 6 months after prescription; (2) an increased risk of suicide for older antidepressants compared with new ones; (3) a higher risk of serious suicide attempt in the first month after starting treatment (however, the highest risk was seen in the month before starting treatment), and (4) an increased risk of serious suicide attempt in adolescents compared with adults, although they had a similar pattern of risk over time [34].

Finally, in medicine a treatment which is helpful to many may be harmful to some [35]. For example, suicidal behavior in depressed youth on SSRI treatment may also be the consequence of unknown bipolar disorder with the induction of mood switches or the aggravation of depressive mixed states [36].

Do SSRIs Have Specific Age-Related Effects?

Since no studies have shown that TCAs can be effective treatments in child and adolescent depression, it should be recalled that major differences exist between the noradrenergic systems (the main target for TCAs) and the serotoninergic systems (the main target for SSRIs) in terms of aminergic system maturation. Animal studies in different species have shown that only serotoninergic and acetylcholinergic systems are mature in newborn animals. The noradrenergic system does not fully develop until nearly adulthood [37–40], whereas the serotonergic and cholinergic systems may be fairly developed at birth [41–43]. Thus TCAs, with their action predominantly based on the noradrenergic system, may be ineffective in young people due to an immature neuropharmacological target. Furthermore, serotoninergic systems play an important role in the differentiation and specialization of cerebral subsystems [44]. In sum, animal studies, without bringing forth any proof, suggest a possible link between psychotropic action and SSRIs in young subjects.

Concerning clinical trials, even though most trials have not shown SSRIs to have a superior efficacy compared with placebo, four studies showed a modest efficacy (though not for TCAs). Also, the few trials comparing drugs support the idea of a superiority of SSRIs in young subjects. In a trial comparing clomipramine with paroxetine, the two drugs demonstrated the same efficacy profile; however, the former is the only TCA with a serotoninergic effect [15]. Moreover, in a trial comparing paroxetine and imipramine against placebo, Keller et al. [18] only found significant effects in patients treated with paroxetine. Again, these two studies suggest the possible antidepressant-specific effect of SSRI compared to TCAs in young subjects.

An indirect way to approach the question of the SSRI antidepressant effect is to evaluate SSRI capacity to induce mood changes in young depressed subjects and/or to worsen the course of depression, as has been shown in adult [35] and in adolescent [45] mixed depression. Very few studies have addressed this question, but I can quote at least two. Biederman et al. [46] reported the follow-up of a young bipolar cohort and studied how mood changed in their patients in relation to prescriptions given at the previous consultation. Only SSRIs induced mood changes or switches in depressed bipolar subjects while TCAs did not. The second study was from a data base analysis of a private American insurance company with more than 7,000,000 subjects. From this population, the authors analyzed the effect of age on the number of manic conversions in 87,920 antidepressant consumers aged 29 years or younger. They found that subjects more frequently declared a manic conversion after SSRI treatment, and that this effect was larger for younger subjects and not seen under TCA treatment. The effect of age on manic conversion frequency appeared solely after puberty onset (the authors did not find this effect in subjects younger than 10 years) [47]. These two studies support

the view that the antidepressant effect of SSRIs is age related, contrary to that of TCAs.

Two other studies also give indirect results about development-related issues. The first one addresses this question within the limits of adulthood, Mulder et al. [48] showed that in depressed young adults (<24 years), serotoninergic molecules led to more remissions than noradrenergic ones. This age-dependent effect was not found in older subjects. The second study, on adolescent depression treatment with an SSRI, showed a correlation between the clinical response quality and the SSRI concentration measured on blood platelets. The correlation may suggest that the pharmacological effect of the SSRI was associated with the clinical response to the drug [49].

Finally, concerning side effects, it should be noted that in few cases SSRIs can have an effect on child and adolescent growth. Weintrob et al. [50] showed that this impact on growth was related to serotoninergic effects on growth hormone (GH) secretion: the effect reversed when the treatment was stopped or when GH was also prescribed. All these facts suggest the existence of a psychotropic effect, though the antidepressant effect is not validated. Of note, the psychotropic effect of SSRIs in children and adolescents is also supported by the use of SSRIs for the treatment of childhood obsessive compulsive disorder [51].

How to Account for the Placebo Effect in Child and Adolescent Depression?

Before addressing the question of the placebo effect in child and adolescent depression, we should recall that a major depressive episode in children and adolescents is not identical to its adult or young adult counterpart. This fact is important since there exist many claims (if sometimes only implied) which might lead one to think that child and adolescent depression is of the same nature as adult depression. Many studies have demonstrated the opposite [for review, see 52]. Here I note only one study with particularly robust methodology. In a prospective birth cohort where risk factors were gathered until the age of 9, Jaffee et al. [53] compared the characteristics of subjects who developed a depression at 11, 13 or 15 years of age versus subjects who developed a depression at 18, 21 or 26 years versus normal controls. The results were unequivocal: the early risk factor profiles gathered were extremely different for the adolescent depression group compared with the young adult depression group. For the adolescent group, authors found more problems after birth, psychomotor retardation, parental instability or separation, criminality and/or psychopathy in the family history as well as conduct and emotional disorders in the subjects' childhood. In the young adult group, the only risk factor occurring more frequently than in the control group was an overrepresentation of sexual abuse experiences in childhood. Thus this study suggests that a major depressive episode affects a heterogeneous clinical group and the age of onset has to be taken into consideration in the understanding of clinical and psychopathological situations.

From this finding, we can consider the placebo effect in child and adolescent depression from two different perspectives: that of therapeutic alliance and that of psychotherapy.

(1) The first perspective concerns the concept of therapeutic alliance as a primary objective in any care given to a child or adolescent, particularly when he or she suffers from a depressive episode [54]. Therapeutic alliance is a familiar concept for pediatric or psychiatric clinicians. In adult populations it has been shown that 'nonspecific' factors may be associated with the improvement of depressive symptoms, no matter whether the 'specific' treatment approach is psychotherapeutic or pharmacological [55, 56]. These factors include formation of a therapeutic alliance, health professionals' empathy, patients' motivation to change and patient compliance. It has been suggested that these factors may explain a significant proportion of the benefit seen in antidepressant trials under placebo conditions [57]. Considering the psychopathology of adolescents, several authors have stressed the importance of such factors in the field of psychiatric treatment [54]. The first encounter with a child or adolescent and his or her family appears to be crucial [58]. One should notice that the risk factors associated with treatment resistance in child and adolescent depression [for review, see 59] are very close to the risk factors associated with poor compliance in the field of pediatric pharmacology in general [for review, see 60]. These include past history of poor compliance [61, 62], family dysfunction or poor parent-child communication [63, 64], short doctor's appointments; parents' dissatisfaction with the doctor, and side effects [61]. When a patient is included in a pharmacological trial, he or she cannot be representative of all depressed youths from a therapeutic alliance care perspective, since we have to obtain written consent from both the child or the adolescents and their parents after careful and complete information has been given. Thus the inclusion of a patient in a trial implies some degree of therapeutic alliance with the patient and

the family. This then becomes a factor for a better prognosis in terms of follow-up, no matter which treatment is given, and may lead to an inflation of estimates of the size of the placebo effect.

(2) The psychotherapy perspective implies that the treatment which is effective in child and adolescent depression is psychotherapy, no matter which method is used. Since the late 1990s, several rigorous studies have been conducted validating the efficacy of psychotherapeutic approaches in child and adolescent depression. Several techniques were evaluated in randomized and controlled trials such as interpersonal psychotherapy [65, 66], CBT [19, 67, 68], family therapies [67, 68] and psychodynamic therapies [69]. We hypothesize that a psychotherapeutic treatment occurs during a pharmacological trial, as a clinician meets the child or adolescent every week, shows an interest in his life, in the impact of treatment, in his current situation and answers his questions: whether intended or not, for the patient this marks the beginning of a psychotherapeutic process with a clinician. Furthermore, appointments are voluntarily fixed on a weekly basis, at least at the beginning of the treatment. These appointments tend to have a significant duration because clinicians have to measure many variables in order to assess clinical progress. The placebo effect response may thus be partially due to the child ending up in an unintentional psychotherapeutic dynamic, irrespective of the orientation of the clinician.

In What Circumstances Should SSRIs Be Prescribed to a Child or Adolescent?

It should be noted that the following discussion applies only to child and adolescent *depression,* since a specific effect of SSRIs on symptomatology has been demonstrated for compulsive obsessive disorder [51]. To summarize what has been discussed previously for child and adolescent depression: (1) non-pharmacological treatments, like psychotherapies, are particularly effective [8]; (2) there are numerous specific psychopathological and social factors in youth depression; (3) SSRIs may have an effective psychotropic action, although this remains to be confirmed and may be limited to certain cases, and (4) we should manage and analyze the risk of suicidal behaviors in depressive pathology more carefully: it is already high, and even more so at the beginning of an SSRI treatment.

From the perspective of clinical experience, and with the goal of avoiding a simplistic and mechanical view-

Table 2. Multimodal framework for evaluation and treatment of child and adolescent depression, including indications of drug treatment (adapted from Cohen et al. [54])

(1)	Manage suicidal risk when necessary Hospitalization and milieu therapy Crisis intervention Sedative drug
(2)	Evaluate child's psychopathology and context Severity of depression Acute or chronic course Comorbidity (e.g. anxiety disorder, borderline personality) History of bipolarity and psychotic symptoms Family environment and social context Psychosocial stressors, including physical and sexual abuse Impact on child's development
(3)	Promote therapeutic alliance with both the child and his/her parents
(4)	Choose appropriate psychotherapeutic approach according to the child's assessment and style Cognitive and behavioral psychotherapy Interpersonal psychotherapy, psychodynamic psychotherapy Family intervention and discuss if psychosocial intervention is necessary
(5)	Consider pharmacotherapy when Severe depression persists Associated psychiatric morbidity exists Psychotherapy is not available Psychotherapy has failed
(6)	Before drug prescription Evaluate patient's and family's acceptance of drug treatment Educate patient and family about drug treatment and possible adverse events
(7)	Choose medication according to documented evidence-based data Fluoxetine (20–40 mg/day) Assess efficacy with frequent follow-up visits (every 15 days) Maintain treatment for at least 3–6 months
(8)	If resistance, consider Hospitalization, milieu therapy or residential treatment Alternate SSRI[a] Clomipramine, or other TCAs, or mianserine, or other recent compound[a] Augmentation treatment (e.g. lithium)[a] Electroconvulsive therapy
(9)	At each stage, continue to provide psychotherapeutic treatment and psychosocial intervention

[a] See Hughes et al. [71] for details on the available augmentation strategies.

point, I will outline the situations in child and adolescent depression which, I argue, warrant complement drug prescription. My experience includes years of clinical practice and research in the treatment of child and adolescent depression, including numerous approaches such as psychotherapy [11], pharmacological treatment [15, 54] and electroconvulsive therapy [13, 70]. I have summarized in table 2 how SSRI prescription can be combined with the evaluation and general care of depressed youths and their family. When medication appears to be required, the data from the literature overwhelmingly supports the use of fluoxetine. Pharmacological treatment needs to be part of a multimodal approach to the patient's morbidity. I would like to emphasize that drug treatment should be combined with appropriate psychotherapeutic and psychosocial interventions, as these may foster better compliance with the treatment plan and eventually better outcome. However, it should be noted that this option does not always fit in with the practical possibilities that our young patients offer.

To return to the initial motivation for the current paper, I do not advocate simply banning SSRI prescription. In a certain number of cases, prescription appears to be useful, particularly in severe and resistant forms of child and adolescent depression when psychosocial interventions and psychotherapeutic approaches have been undertaken or are not possible. The formation of a therapeutic alliance is the *primum movens* in the treatment of a depressive youth. All aspects of the patient's psychosocial background should be considered, as they may account for both poor treatment outcome and poor compliance. With each depressed child or adolescent, the clinician's intervention should encompass restoring self-esteem or narcissism, being open to transference movements that may be intense at the first meeting, and providing a 'positive mirror' [54]. However, given (a) the inflationist trend to prescribe SSRIs to anyone at any age, particularly to young subjects, and (b) the importance of clinical experience with children and adolescents to manage the therapeutic approach within the above multimodal perspective, I argue that prescription should be given to this age range by specialists well trained in child and adolescent psychiatry.

Acknowledgment and Disclosure

I would like to thank Christophe Huynh and Anna Wilson for their very helpful comments on the manuscript. I have been an investigator in two pharmaceutical trials funded by SmithKline Beecham (DEROXADO) and Sanofi-Synthélabo (DEPAKOTE). I am also currently conducting a naturalistic follow-up study of youths with bipolar I disorder; the study is financed by Sanofi-Synthélabo.

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