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Selective serotonin reuptake inhibitors: use in children and adolescents with major depressive disorder

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Treatment of depression in children and adolescents is a health care question of primary importance and it is presently associated to significant social concern. In recent years some studies have appeared that throw light on the question of the use of antidepressants in these sectors of the population in which they have been used. Information provided by national agencies, associations of health professional's guidelines and other publications have been reviewed. The results show an increase in aggressive and desinhibitional behavior, irritability, self-injuries and an increase in suicidal motivation with the use of antidepressants in children and adolescents. It can be added that no completed suicides have been recorded. Proof of antidepressant effectiveness only appears in the case of fluoxetine for moderate to severe depressions in children and adolescents and for tricyclic antidepressants in adolescents. The important methodological difficulties and the lack of studies only allow to consider the results as exploratory and it is hard to obtain definitive clinical results, however, they are useful to guide future investigation.

Key words:
Antidepressants. Selective serotonin reputake inhibitors (SSRI). Children. Adolescents. Major depressive. Suicide.

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Utilización de antidepresivos inhibidores selectivos de la recaptación de serotonina en niños y adolescentes con depresión mayor

El tratamiento de la depresión en niños y adolescentes es una cuestión sanitaria de primer orden y actualmente asociada a elevada alarma social. En los últimos años han aparecido estudios que ponen en cuestión el uso de los antidepresivos en estas poblaciones del modo en que se ha estado realizando. En este trabajo analizamos la información proporcionada por los organismos oficiales y por las principales revisiones publicadas sobre el tema. Los resultados muestran un aumento del riesgo de desinhibición conductual, irritabilidad, conductas agresivas, autolesiones e incremento de ideación suicida con el uso de los antidepresivos en niños y jóvenes. Se puede añadir que no se han registrado suicidios consumados. Hasta el momento actual sólo disponemos de pruebas de eficacia antidepresiva en el caso de fluoxetina para depresiones moderadas-graves en niños y adolescentes y para los antidepresivos tricíclicos en los adolescentes. Las importantes dificultades metodológicas y la escasez de estudios sólo permiten considerar los resultados como exploratorios y es difícil extraer conclusiones clínicas definitivas, pero son útiles para guiar la investigación futura.

Palabras clave:
Antidepresivos. Inhibidores selectivos de la recaptación de serotonina (ISRS). Niños. Adolescentes. Depresión mayor. Suicidio.

INTRODUCTION

Prescription of antidepressants has become common in the psychiatric practice. It is the drug treatment of choice for depressive disorders of adult patients and they are commonly used in other diseases where they have demonstrated clinical efficacy (generalized anxiety, panic disorder, obsessive-compulsive disorder, among others). Furthermore, better knowledge on its management has encouraged doctors to prescribe them in situations for which they have not been officially approved, for example in conditions related with impulsiveness problems or in refractory painful pictures. Their use has also been extended in major depression in the children and adolescent population, partially due to the need to seek effective therapeutic alternatives, although antidepressants still do not have an official indication for this in this population in our country.

Prevalence of depression in children is approximately 2%, a value that increases to 4% to 6% in adolescents[1] and accounts for an important morbidity and mortality cause given the association existing with suicide, which is the third cause of death in this age segment[2]. Furthermore, in addition to the suffering that this causes the patient, it provokes a serious public health problem due to the resulting important use of resources on the primary and specialized level.

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Given the great variability of clinical expression of depression, its multifactorial etiological character and the great weight that the emotional and environmental factors have in the origin and development of some depressions, the existence of non-drug therapeutical alternatives should be kept in mind. This is true mainly in mild and moderate depressions, since this is where the environmental and psychobiographic factors have the most importance.

In spite of the difficulties of applying a «medical evidence based» methodology in the analysis of efficacy of psychotherapeutic and psychoeducative techniques[3], there are some studies that evaluate the efficacy of psychotherapeutic interventions in child-adolescent population with mild-moderate major depression that provide favorable results and, in some cases, even have a positive balance greater than drug treatment[4]. Even the clinical practical guidelines of the National Institute for Health and Clinical Excellence published in September 2005[5], in which therapeutic recommendations are separated according to seriousness of the disorder, applying ICD-10 criteria, recommend the use of psychotherapeutic techniques and not antidepressants as the first line of treatment in children and adolescents with mild depression. It also indicates that in the cases in which psychodrugs are recommended, these should always be used in combination with psychotherapies. However, the fact that the real accessibility to treatment is generally an important limiting factor should be kept in mind.

Being able to use the most accessible and efficient treatments has become one of the recent most important challenges for the health care professionals in the management of major depression in the young and adolescent population. In this sense, antidepressants have been considered a reasonable alternative in recent years, given the seriousness of the disease and the need to administer a treatment that can control the symptoms, mainly in the case of serious major depressions and with risk of suicide. The problem has occurred when research in recent years has questioned the use of antidepressants in children and adolescents[6]. In effect, the increase of behaviors associated to suicide and lack of evidence on the efficacy of these treatments has generated doubts on the safety of these drugs and the social concern has been reflected in the mobilization of scientific institutions and governmental bodies[7]. The objective of this article is to analyze the most relevant information available on the use of antidepressants in children and adolescents in order to orient clinical decision-making and contribute to the better use of these drugs.

METHODS

Publications of the Cochrane group and of regulatory organisms on the use of drugs of different countries have been reviewed: Food and Drug Administration of the USA (FDA)[8], American College of Neuropsychopharmacology (ACNP)[9], Australian Drug Evaluation Committee (ADEC)[10], Health Canada[11], Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA)[12], European Medicines Agency (EMEA)[13] and the Spanish Agency of Drugs and Health Care Products (AEMPS)[14]. A search in Medline was also done, choosing meta-analysis and systematic reviews.

RESULTS

The main characteristics of the systematic reviews and meta-analysis analyzed are summarized in table 1 and the main conclusions of the official bodies and institutions are synthesized in table 2.

Within the Cochrane group for the study of depression, anxiety and neurosis, Hazell et al.[15] published a review of the controlled and randomized trials that compared the efficacy of tricyclic antidepressants versus placebo in child-adolescent depression. The results obtained suggest that the use of tricyclic antidepressants in prepuberal stage is not justified and that, although there is some evidence on the efficacy of these drugs in depression of adolescents, the size of the effect is, in all, moderate.

The MHRA, English agency in charge of regulating drugs, reviewed 13 randomized, double blind, placebo controlled clinical trials[16] (2 with fluoxetine, 2 with sertraline, 3 with paroxetine, 2 with citalopram, 2 with venlafaxine and 2 with mirtazapine). They found no evidence of efficacy for child-adolescent major depression of these drugs but there was an associated risk of more ideation and suicidal gestures. The benefit/risk balance was unfavorable for paroxetine, venlafaxine, sertraline, citalopram, escitalopram and mirtazapine. It was not possible to know the profile of fluvoxamine given the absence of studies in the pediatric population. Only fluvoxamine demonstrated its efficacy in the treatment of depressive disease. However, like the rest of the SSRI, it was also associated to a mild increase of self-injury behaviors and suicidal thinking. Therefore, the Committee on Safety of Medicines (CSM) of the MHRA[17] contraindicated the initiation of new treatments with the drugs mentioned except for fluoxetine. If the patient was improving with any of them, ending the ongoing treatment was considered as an acceptable recommended option.

After an extensive review of the information supplied by 24 trials that enrolled more than 4400 patients, the American FDA[18,19], determined the obligation of including a «black» label that warned about the increase in of ideation and self-injurious behavior associated to the use of any antidepressants. The analysis showed greater risks of behaviors associated with suicidal risk during the first months of treatment (4% in the patients treated with the antidepressant, twice that in the placebo group) and hostility or agitation reactions (13,4% in regards to placebo). No suicide was re-

Table 1 Summary of systematic reviews and meta-analysis

	No. of studies	No. of patients	Age	Drugs	Conclusion
Hazell (up-date) et al., 2005	13	506	6-18 years	Tricyclic antidepressants (TCD)	TCDs have shown a similar response to placebo in prepuberal subjects In adolescents, a response superior to the placebo was observed, but with moderate magnitude
Jureidini et al., 2004	6	941*	6-18 years	Fluoxetine Sertraline Paroxetine Venlafaxine	Sufficient evidence does not exist that the clinical benefit compensates the risks of SSRIs versus placebo
Whittington et al., 2004	5 studies published. Unpublished data provided by the Drug Safety Committee of the United Kingdom	911 included in published studies	5-18 years	Fluoxetine Paroxetine Sertraline Citalopram Venlafaxine	The published data suggest a favorable profile for SSRI, but only fluoxetine maintains the positive balance when the unpublished data are added Using venlafaxine and SSRI in child-adolescent depression should be advised against except in the case of fluoxetine
Courtnay, 2004	5 (the same as Jureidini)	See Jureidini			The methodology problems observed in the different studies are a limitation to generalize their conclusions
Cheung, 2005	8 studies published and unpublished data	2.911	6-18 years	Fluoxetine Paroxetine Sertraline Citalopram Venlafaxine Mirtazapine Nefazodone	The great variability in methodology of the studies could explain the different results. There is no evidence that make it possible to differentiate between the different SSRIs
Hammad**, 2006	24 (16 studies on major depression)	4.582	They are pediatric patients, but age range is not specified	Bupropion*** Citalopram Fluoxetine Fluvoxamine*** Nefazodone Paroxetine Mirtazapine Sertraline Venlafaxine	The use of antidepressants in pediatric patients was associated to an increase of risks of behaviors or thoughts related with suicide, having moderate magnitude

*Treated with selective serotonin reuptake inhibitors (SSRI) or placebo.** In this study, aspects related with safety (behaviors related with suicide), and not with efficacy, are evaluated. ***There are no studies in major depression with these drugs.

corded. As in other analyses, only fluoxetine was considered to have evidence of efficacy in child -adolescent major depression.

In the review conducted by ACNP[9], 15 placebo controlled, double-blind and randomized published and unpublished studies were included (it contains those reviewed by the MHRA), in over 2000 young people with major depression. Two of the studies were conducted with fluoxetine, 2 with citalopram, 2 with mirtazapine, 2 with nefazodone, 3 with paroxetine, 2 with sertraline and 2 with venlafaxine. In the case of fluoxetine, sertraline, paroxetine, citalopram and nefazodone, these demonstrated depressive efficacy in at least one comparative and randomized comparative study (PCR) conducted in this population. Thus, they were assumed to be effective drugs in the treatment of major depression in children and adolescents. They considered that the discrepancies in the results obtained, in regards to other analyses, are probably caused by different methods and they recommended additional studies. Regarding the risk of

Table 2 Main conclusions of the regulatory bodies and agencies on the efficacy and safety of the new antidepressants

Institution	Conclusions
MHRA (United Kingdom)	Unfavorable benefit/risk balance for: paroxetine, venlafaxine, sertraline, citalopram, escitalopram and mirtazapine Only fluoxetine demonstrated efficacy in the treatment of depression, although, as the above-mentioned antidepressants, a mild increase in self-injurious behaviors in suicidal thinking was associated
FDA (USA)	Greater risk of behaviors associated with suicide and reactions of hostility and agitation with antidepressants than with placebo during the first months of treatment. Only fluoxetine showed efficacy in the treatment of depression. (This is approved for children > 7 years)
American College of Neuropsychopharmacology (USA)	The SSRIs may be effective in child-adolescent depression, although there are methodological limitations in the study is available The potential increase of suicide risk associated to these drugs is not confirmed
EMEA/ AEMPS (Europe/Spain)	Greater risk of suicidal behavior and hostility with SSRI, duloxetine, mianserin, mirtazapine, reboxetine or venlafaxine than with placebo Only fluoxetine demonstrated efficacy in the treatment of depression. Only fluoxetine has demonstrated a favorable benefit/risk balance. Its authorization is approved

suicide, they stated that the data obtained from the clinical trials, from immunological and autopsy studies, do not confirm the possible increase of possible suicides motivated by the use of the mentioned antidepressants in the child-adolescent population under treatment for major depression (MD). The ACNP found no objection to continuing to use both SSRI and new generation antidepressants as effective and accessible psychopharmacological treatment in children and adolescents for the treatment of those cases of major depression that required it due to their seriousness.

In the review conducted by the Committee of Drugs for Human Use (CHMP) of the European Drug Agency (EMEA)[20,21], and the risk-benefit balance of the use of the SSRI in children and adolescents, the following drugs were included: citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, mianserin, mirtazapine, reboxetine and venlafaxine. They found that suicidal behavior (suicide attempt and suicide ideation) and hostility behavior (basically aggressive behavior) occurred more often in the group of children and adolescents treated with these antidepressants versus the group that received the placebo. Only fluoxetine demonstrated moderate antidepressant efficacy. They concluded that the antidepressants mentioned should not be used in children and adolescents, except in the specifically authorized therapeutic indications. They suggested that in isolated cases, when due to an individual clinical need the doctor makes the decision to use these drugs for the treatment of depression or anxiety in this age group, that a very close follow-up should be done due to the possible appearance of suicidal behavior, self-injury or hostility, especially during the beginning of the treatment.

Recently, the EMEA has issued a favorable ruling to extend the indication of fluoxetine to children of 8 years or more and adolescents with moderate to severe depression who do not respond to psychotherapy, based on a rigorous evaluation of the data available on the use of fluoxetine in children and adolescents with major depression[22].

The application and distribution of the conclusions of the CHMP of the EMEA in Spain are done by the AEMPS. Health care professionals in our country have been maintained informed by this institution and by common channels on all the process, using informative notes in the web pages of the AEMPS[23,24]. Furthermore, the distribution has been done in the respective Regional Communities by their corresponding organizations. In the case of the Madrid Community, it was done with the RAM Bulletin of the Pharmacovigilance Center of the Madrid Community[25].

The last informative note of the AEMPS, on June 6, 2006, reported that the experts' review of the EMEA provided a benefit/risk balance that was favorable for the use of fluoxetine in child-adolescent depressent[24]. Formal authorization is still pending by the European Committee before the indication can be approved in Spain. In any event, its use in this situation should be considered under the following conditions:

- In moderate to severe depression.
- In adolescents and children of 8 years or more.
- If the depression does not respond to psychotherapy after 4-6 sessions.
- In combination with psychotherapy.

- At the initial dose of 10 mg/day, which can be increased to 20 mg/day after 1-2 weeks of treatment.
- Monitoring the suicidal behavior closely, especially during the beginning of treatment.
- Considering that treatment should be re-assessed if no clinical benefit is obtained after 9 weeks.

Furthermore, the authorities establish that the laboratory having the marketing authorization should perform additional studies to assure that the safety of fluoxetine in this population group remains acceptable.

According to that mentioned previously, fluoxetine would be the only drug, among the new generation antidepressants and SSRIs, authorized for the treatment of depression in children and adolescents. It should be remembered that the legally foreseen procedures (clinical trials or compassionate use[26]) should be followed for use of drugs in unauthorized indications. This latter procedure should be restricted to isolated patients and in rare circumstances, when the doctor considers the use of the drug essential. The informed consent of the patient or his/her legal representative and a clinical report in which the doctor justifies the need of such treatment is essential, it corresponding to the regulatory administration to know, authorize and supervise this action.

In addition to the analyses and reports made by the different Regulatory Agencies, there are several independent studies that evaluate this problem. In the following review, we explain those that have had greater weight on the decisions adopted. The meta-analysis made by Jureidini et al. in 2004[27] reviewed 7 controlled studies (PRC) (3 with fluoxetine, 1 with paroxetine, 2 with sertraline and 1 with venlafaxine) that included a total of 477 patients treated with antidepressants versus 464 treated with placebo. None of the studies presented data on the self-injury rate and they did not record any cases of consumed suicide. It is pointed out that the rarely appearing adverse events (such as suicide) are difficult to detect in randomized controlled trials. They found data of significant efficacy of the placebo that was only exceeded by that of antidepressants in some of the measurement variables used. Thus they concluded that the efficacy aspiration of antidepressants could have been exaggerated by the authors and they questioned the independence of the results due to the sponsorship of the clinical trials by the pharmaceutical industry. They did not find sufficient evidence that these drugs provide clinical benefit for the group of patients being studied, so that they did not consider their use as antidepressants recommendable in this population.

This systematic review made by Whittington et al. in 2004[6] analyzed the data published and unpublished of the trials in which any antidepressants had been compared with placebo in child-adolescent depression. They selected 5 PCR trials published (2 with fluoxetine, 1 with paroxetine, 2 with sertraline) that passed some methodological quality criteria and they re-analyzed the data used by the CSM of the MHRA of the United Kingdom. They used the CMS registries to obtain unpublished trials (fluoxetine, paroxetine, sertraline, citalopram and venlafaxine). They assessed the efficacy results (symptom remission, response and score on depressive symptom scale) and safety results («suicidability» serious adverse reactions and drop-out from treatment due to adverse events). The authors concluded that only fluoxetine maintained a positive balance when the unpublished data are included, even though the data published suggest a favorable profile of SSRI in the treatment of child-adolescent depression. Regarding suicide risk, they also indicated that the existing studies have not been designed for its assessment (the statistical analysis of rare events and small samples may include Type I and II errors). They accepted that the suicide risk may be real, either due to the major depression itself or to the onset of antidepressant treatment. They concluded that, given that there is no clear proof of efficacy but that there is an increase in «suicidability», the use of these drugs in children and adolescents should not be recommended, except in the case of fluoxetine.

In another study, also in 2004, done by Courtnay[28], the results of the same clinical trials analyzed by Jureidini[24] were review and they included the comments and contributions made by this author. It indicated that only two SSRIs, fluoxetine and sertraline showed statistically significant results in the main efficacy endpoints. They stress that the results of sertraline were based on the combination of the data supplied by two independent studies in which the drug was not more effective than a placebo. They observed several methodological problems and biases that significantly limit the important weight of the conclusions, mainly stressing inclusion and exclusion biases and the use of insufficiently standardized methods and a short follow-up time as well as absence of stratified analysis with a small sample size.

In 2005, Cheung et al.[29] made a review of the clinical trials published and of unpublished data on child-adolescent depression available in December 2004. Based on their analysis, they concluded that the studies available had high variability of methodology and that this may be the cause of the possible difference between the results obtained in the response to the active drug or placebo and that there was not evidence that made it possible to differentiate between the different SSRIs. They found a clear relationship between the use of the drugs and the adverse reactions.

In March 2006, Hammad et al. published a review to assess the relationship between the use of antidepressants and behaviors or ideas related with suicide in pediatric patients[30]. They included 24 placebo controlled clinical trials in which the patients were treated with the following antidepressants: fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine, venlafaxine, mirtazapine, bupropion or nefazodone. Sixteen studies included patients with major depres-

sion. Data were obtained from 20 studies to analyze adverse reactions related with suicide. No case of suicide was recorded. The relative risk for SSRI in trials on depression was 1.66 (95% CI: 1.02-2.68) and for all the active ingredients considered in all the indications (depression, generalized anxiety disorder, hyperactivity attention deficit and social anxiety disorder), it was 1.95 (95% CI: 1.28-2.98). Table 3 shows the relative risks for each one the active ingredients.

DISCUSSION

No data has been found in favor of the efficacy of the SSRI antidepressants in the child and adolescent population except for with fluoxetine[6,27,28] and four tricyclic antidepressants and adolescents[15]. The problem is in relationship to the prescription of SSRI in young people basically arises from this lack of evidence since the fact that there is an increase in irritability and disinhibition associated to the onset of treatment is not different from that found in adults. In any event, it should be remembered that the FDA warns that the current lack of evidence in favor of the efficacy should not be interpreted as a demonstration of its lack[19]. On the other hand, in some studies it has been observed that the capacity of SSRI in adolescents does not seem to be different from that shown in adult patients[29] in whom 50% of the studies are not favorable. Furthermore, more studies are needed to obtain the two positive results required by the regulatory agencies to obtain the authorization of the indication. For this reason, the need to have a greater number of studies to be able to reach these two positive trials also required in the case of young patients should not be surprising[29].

On the other hand, the meta-analytic comparisons must be considered with caution, given the heterogeneity that exists between the studies conducted and the significant existing methodological limitations[28,29]. These could justify the differences that exist in the efficacy of the placebo, that range form 33% to 60%[26], mainly in those studies with a smaller sample size and that have been done as multicenter studies. It is important to mention that the studies that show differences with the placebo are those in which there is less response to the placebo, however, there is not a greater response to the drug. The response to placebo is characteristics of children and also of depression, this not being seen so strongly in diseases with greater organic base. This consideration is consistent with the fact that the positive results mainly appear in those studies that include cases with greater severity of the symptoms and thus with less response to placebo. There are diverse variables that reduce the statistical power of the conclusions of the meta-analysis studies related with the subject, among them the experience of the investigators and clinicians involved and the different inclusion and exclusion criteria used by the different sites standing out (age, psychiatric background of the subjects, previous or current treatments, acceptance of hospitalized patients, enrolment sources, duration of the evaluation, etc.).

Another aspect to consider is that the doses used are extrapolations of those used in the adults. Thus, they may not be suitable for the target population[32]. Unfortunately, there are no studies that make it possible to know the adequate dose range for children and adolescents. In the same way, the scales used for the evaluation are mostly only valid for adults[28]. Furthermore, each one of the studies has one variable of principal measurement and several secondary ones that frequently show contradictory results. It should be considered that the regulatory agencies only use the principal measurement to make their recommendations.

The presently presented may have some relationship with the fact that the difference of global efficacy between antidepressants and placebo is poor in this age group[29] according to that affirmed in the results of the available studies. Due to the situation of poverty in the differentiation of efficacy regarding the placebo, the fact that both the SSRI and most recent antidepressants are associated to greater frequency of suicidal behaviors and ideas in the first moments of treatment is acquiring greater importance although it has not been possible to confirm consumed suicides[9]. This lack of compensation in balance between efficacy and adverse reactions is that which would have led the regulatory bodies to indicate the unfavorable balance for most of the antidepressants, with the exception of fluoxetine, in the treatment of depression in the child-adolescent population[10,11,19,21,23].

Table 3 Relative risk of suicidal behavior of different antidepressants versus placebo

Drug	Relative risk (95% IC)	
	Trial on major depression	All the trials, all the indications
Citalopram	1.37 (0.53-3.5)	1.37 (0.53-3.5)
Fluvoxamine	There are no trials	5.52 (0.27-112.55)
Paroxetine	2.15 (0.71-6.52)	2.65 (1-7.02)
Fluoxetine	1.53 (0.74-3.16)	1.52 (0.75-3.09)
Sertraline	2.16 (0.48-9.62)	1.48 (0.42-5.24)
Venlafaxine (retard formulation)	8.84 (1.12-69.51)	4.97 (1.09-22.72)
Mirtazapine	1.58 (0.06-38.37)	1.58 (0.06-38.37)
Nefazodone	There are no behaviors related with suicide	There are no behaviors related with suicide
Bupropion	There are no trials	There are no behaviors related with suicide

On the other part, there are also data that point in the direction that the theoretical increase of suicide risk is not accompanied by a real increase in suicide[9]. In fact, the mentioned increase in suicide risk is based on very varied data, some of which mention irritability, disinhibition, or emotional lability and only a few mention increase of suicide ideation. Some epidemiological studies suggest that the use of SSRI and other antidepressants have reduced the real risk of suicide, this being associated in some countries over the last 15 years to a 33% reduction in the suicide rate of young persons, coinciding with the generalization of drug use. An example is the downward tendency recorded in Japan in the year following the marketing of the SSRIs[9]. Other authors also find an inverse relationship between treatment with antidepressants and adolescent suicide[34]. Furthermore, some studies suggest that combining psychotherapy interventions could decrease suicide risk associated to the use of SSRIs, given that the association of cognitive-behavioral therapy (cognitive-behavioral therapy (CBT) and fluoxetine increases the global positive balance and significantly reduces suicidal ideation[35]. In fact, several studies conducted on an adolescent population support the efficacy of cognitive-behavioral therapy (CBT), although they also admit that there are 40% of non-responders and that accessibility is limited in many countries[9].

As can be observed, the results are not always in agreement and do not allow final conclusions to be drawn. The recordings of adverse reactions are mostly obtained from spontaneous reports of the patients or relatives, while a systematic collection of the events with the Standardized Side Effects Checklist was used only in a multicenter study with fluoxetine[36]. Regarding suicide behaviors, there is also no consensus in the terminology used regarding the behaviors associated to suicide. Thus, the different studies include different concepts in this section. It is precisely in regards to suicide where the task is very complicated since these ideas and behaviors form a part of the clinical picture that is being treated and it is often the opinion of the clinician that can relate the appearance of a certain adverse effect with the medication or with the baseline situation of the disease.

Another factor that makes interpretation of the results difficult is the policy of publishing sponsored studies by the pharmaceutical companies. In fact, there is a clear bias towards not revealing negative findings[37]. This behavior has motivated the International Committee of Medical Journal Editors[38] to demand prior registration for those who want to publish the results of clinical trials and to recommend the same publication policy to other publishers. This is a serious problem of clinical drug research. Precisely, different sources have underlined the distortion of the results obtained by studies that were financed with funds coming from pharmaceutical companies[39,40,41].

On the other hand, other problems associated to the use of SSRI are also arising at this time. Among them is the questioning of their harmlessness on neuropsychological development or insistence on using caution in their use by mothers prior to giving birth or during breast-feeding. Symptoms of drug withdrawal have been detected in newborn born from treated mothers[42] and there is firm suspicion on the possible involvement of antidepressants in epileptic episodes in newborns, and on their potential effect on neurocognitive development and neuroplasticity[43]. Recently, a health care alert on the possible teratogenic risk associated to the use of paroxetine during the first quarter of pregnancy was reported by the FDA[44].

Finally, it can be stated that based on the existing data, the decision to use drug treatment can only be individualized based on the risk involved in the disease and the symptoms to be treated and due to the failure of psychotherapy. If an antidepressant must be administered, it should be kept in mind that fluoxetine has shown a favorable benefit/risk balance and that, if used, the patient should be closely monitored, above all at the beginning of the treatment.

CONCLUSIONS

Antidepressants, in the field of mental health of children and adolescents, should be used individually and always within an integral approach. They should be used only in those cases in which the seriousness of the picture requires it and within health care prudence.

According to the existing data, the most favorable benefit/risk balance is for fluoxetine. Less consistent data indicate that sertraline, citalopram and, in adolescents, tricyclics could be used as their second choice.

The studies done up to now do not make it possible to draw final conclusions on the use of other SSRIs and other antidepressants in the child and adolescent population. They need to carefully interpret the results published and to consider the effect of publication bias regarding unpublished material becomes manifest.

Suicide risk should be monitored and evaluated in all cases, but above all in the first weeks after the beginning of treatment with antidepressants. Specific studies with adequate methodology should be done to know the influence of antidepressants and phenomena such as suicide (of rare appearance).

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