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abstract

Objectives: the relationship between antidepressants and suicide has been a controversial issue since the onset of their use, especially in some groups of the population such as children, adolescents and young adults. Today the widespread use of these drugs obliges us to review the existing evidence regarding the issue and to reassess current recommendations. **Methods:** a critical review based on the evidence from clinical trials and observational studies on antidepressants and suicide consulted on Medline, and databases of the FDA and EMA as of 30 September 2010. **Results:** although uncontrolled studies show a positive correlation between the prescription of antidepressants and the reduction in the rate of suicides in the majority of countries, other types of studies with a lower risk of bias, such as meta-analyses of clinical trials and observational studies, warn of a possible increment in the risk of suicide in patients, especially children and adolescents in the first few weeks of treatment. **Conclusions:** until future studies definitively clarify the nature of the relationship between antidepressants and suicide, the recommendation is to strictly comply with the approved indications, ensure close follow-up, and avoid uncontrolled and indiscriminate use of these drugs, which may put these patients under risk. Psychotherapy still remains the elective option in the case of mild and moderate depression, both in children and in adults.

Suicide and antidepressants

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Suicide as a clinical phenomenon

Throughout history the concept of suicide has evolved from a mere isolated act to a notion that forms part of a more ample and complex phenomenon such as a behaviour type[1]. It has been proved that it is the result of a confluence of factors of a diverse kind (social, cultural, psychopathological and biological) which in combination may generate self injurious behaviour varying from transitory ideation up to consummated suicide[2]. When studied under a medical model, it can be affirmed that suicide relates to some specific disorders, in which a series of factors can increase the probability of its consummation whereas others may reduce that probability.

Epidemiological studies in adults show that between 90% and 98% of suicidal patients suffered from some sort of mental disorder[3]. This has been ratified in suicidal adolescents, in which 90-94% of the cases could have been diagnosed of a probable or definitive psychiatric disorder[4]. Of these, the majority were not under treatment when suicide was committed[5,6].

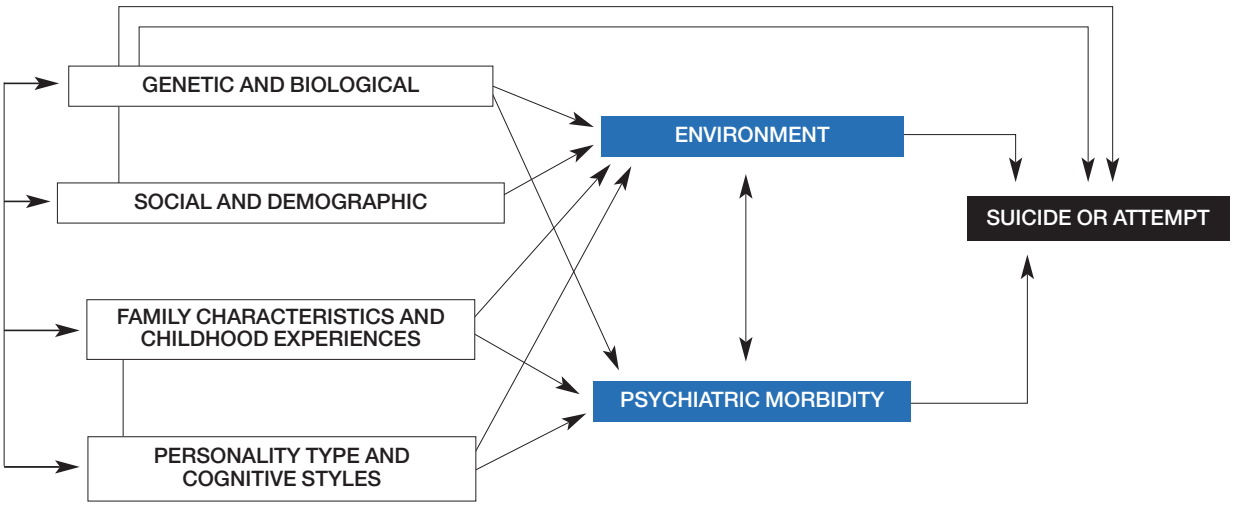
The most frequent psychiatric disorders related to suicide include depressive disorders, schizophrenia and disorders related to the consumption of alcohol or other substances[7]. It is not rare to find a concurrence of various disorders in a single patient, a condition that would significantly increase the risk of self injury.

Suicide in numbers

For methodological reasons it is difficult to evaluate the evolutive tendencies of suicidal behaviour during long periods of time (mainly due to difficulties in identifying and registering cases or due to conceptual changes). According to the WHO, the rates of suicide in the world may have increased to about 60% in the last 45 years, a tendency seen both in the developed and developing world[8]. Traditionally the highest suicide rates have existed among elderly men. However since 1984, a notification was made on the change in tendency. In young people the rates have increased up to the point where currently this group poses the highest risk in one-third of the countries worldwide *(data from the WHO,* 2003).

On national level, external or unnatural causes took sixth place among the main causes of death in Spain in 2008 according to a publication of the National

Suicidal risk factors. Conceptual model.



Beautrais, 1996.

Institute of Statistics released in March 2010. Among these causes, suicide is the most frequent external cause of death, with a total of 3,421 cases. Even though the numbers are similar to the previous year, a reduction in the number of accidents placed suicide in first place. That same month, the Government of Navarre made public the data related to the main causes of unnatural death in 2009. Once again suicide took first place accounting for 55 deaths (8.7 cases per 100,000 inhabitants).

Depression is the main disorder associated with suicide. Previous suicide attempts and severity of the episode are the most important predictors

SUICIDE RISK FACTORS
IDENTIFYING RISK FACTORS

1. Previous and current mental health diagnosis. Affective disorders, schizophrenia, substance abuse disorders.
2. Organic disease: malign tumours, HIV, peptic ulcer, hemodialysis, chronic pain, functional abnormalities including brain damage, multiple sclerosis, temporal lobe epilepsy.
3. Personal history of suicidal behaviour.
4. Family history. Suicides or suicide attempts in first degree family. Mental health problems in the first degree family.
5. Acute and chronic psychosocial stress: loss (in interpersonal relations, work, physical or social status), economic dificulties, legal problems and problems within the nuclear family).
6. Specific problems: anhedonia, impulsiveness, desperation, anxiety/panic, global insomnia and imperative hallucinations.
7. Child trauma: physical and/or sexual abuse, self neglect, parental loss.
8. Demographic characteristics: men, elderly, divorced, widower or single.

Source: Comportamientos suicidas. Prevención y tratamiento. Ed. Ars Médica. 2004

SECONDARY PREVENTION OF SUICIDE
THE MOST EFFECTIVE STRATEGIES

1. Antidepressant medications (with the mentioned precautions).
2. Psychotherapy: interventions regarding suicidal ideation and acts, resolution of problems, and interventions on psychiatric disorders associated with suicide (depression, alcoholism).
3. Psychosocial interventions and close follow-up.
4. Restriction of access to specific suicidal methods: use of antidepressants of lower lethal potencial, installation of catalysts in motor vehicles, barriers in areas of high incidence of suicides, control of arms, etc.
5. Responsible management of the information on suicide in the news media (TV, internet, social networks).

Source: Ganz D, Braquehais MD, Sher L, 2010 Secondary Prevention of Suicide. PLoS Med 7(6): e1000271. doi:10.1371/journal.pmed.1000271

Suicide and depression

It has been proposed that mood disorders, and particularly depression, are the main causes of the majority of the cases of consummated suicide, whether they occur in primary depressive disorders or in patients with other primary illnesses presenting depressive symptoms[9]. From epidemiological data, it has been observed that on average one of every two persons who commit suicide had suffered from some depressive disorder[10]. Of all the factors studied, it appears that suicide attempts are the most potent predictors of new attempts and consummation[11], along with severity of the depressive episode[12]. With regard to treatment and prevention, the evidence indicates that an effective measure is the correct management of the underlying disorder[13].

Use of antidepressants

Since the onset of their use, emphasis was made on close follow-up of the patients during the first few weeks of treatment, probably due to the greater risk observed during this period.

With the introduction of fluoxetine in 1987, the era of the selective serotonin reuptake inhibitors (SSRI) commenced. During the following years, there was a rapid development of new drugs within the group, such as the serotonin-norepinephrine reuptake inhibitors (SNRI). New indications of these drugs were introduced beyond the realm of affective and depressive disorders. The popularity of these drugs was further driven by the perception that they were safe and better tolerated than their predecessors, for example tricyclic antidepressants which are highly lethal in case of overdose.

All this contributed to the expansion of their use. In many countries, a correlation was observed between the increase in the prescription of these drugs and the decline in the suicide rates[14,15]. However, in some other countries the contrary or no effect on suicide rates was observed[16]. None of these studies showed a causal relation, where other uncontrolled factors could also influence the outcome (drug use, prevalence of psychiatric disorders, unemployment, wars), though in general, the results pointed towards a protective effect of antidepresants with regard to suicide.

The controversy starts

However a short time after the introduction of SSRIs, several publications appeared indicating that these drugs could be possible inducers of suicidal ideas in patients under their treatment. Initially they were case studies. Given their methodological characteristics, these studies do not show a causal relation, but they can serve to generate hypothesis, which later could be tested in controlled studies.

In 1990 *Donovan and cols.*[17] described six cases of patients under recent therapy with fluoxetine, in which treatment was discontinued due to the appearance of suicidal ideas. We find a number of factors that could lead to bias. Among these, we point out that the majority of these patients had a history of suicidal ideas or attempts (which is an already known risk factor), a poor response to previous treatments (electroconvulsive therapy, monoamine oxidase inhibitors, MOI) which prolonged the duration of the episodes, comorbidity with other psychiatric and neurological disorders (alcoholism, bipolar disorder, epilepsy, cerebral tumour), high-dose fluoxetine was used (4 out of 6 patients were taking 60-80 mg), important side effects were observed and the use of more than one psychiatric drug was found in the majority of the cases.

In 1999 a second study was published entitled *"The occurrence of suicide following the prescription of antidepressant drugs"*[18] where a retrospective analysis was made of 222 suicide cases between 1990 and 1994 in three regions of England and Ireland. Of these, 18.5% occured during the first month of treatment with the antidepressant. The conclusion was reached that for the same given period, the risk of suicide associated with SSRIs was greater than with tricyclic antidepressants. The same authors suggested a bias which was the lack of randomization in the prescription of these drugs, so that the more severe patients were most probably prescribed SSRIs. They stated that the motive for this could be explained by the avoidance of tricyclic antidepressants given their potentially lethal consequences in case of overdose when compared to the new antidepressants. The authors underlined that the real intention of the study was to show that it was not sufficient to prescribe less dangerous drugs, but it was necessary to implement other measures to reduce the risk of suicide in depressed patients, given that even in this group there are cases of consummated suicide.

In 2000, the FDA *(US Food and Drug Administration)* carried out an analysis of the data on the use of antidepressants in patients diagnosed with depression, not finding significant differences with regard to suicide when comparing the groups under antidepressant therapy and placebo[19].

Children, adolescents and young adults

In 2003, the FDA included fluoxetine in the recommendations for the management of severe depression in children and adolescents, the first SSRIs indicated in the treatment of this disorder in these age groups.

A few months later the *"Committee on Safety of Medicines"* in the United Kingdom issued a contraindication of paroxetine (June 2003) and venlaxafine (September 2003) in patients under 18 years of age with Major Depressive Disorder, considering the possible relation between both paroxetine and venlafaxine, and the suicide attempts observed in the children and adolescents. The FDA had published a warning regarding this issue, recommending avoidance of this drugs within these age groups and reminding clinicians of the need for close monitoring of the patients with greater risk.

Towards the end of 2003, in the United Kingdom, the MHRA *(Medicines and Healthcare Products Regulatory Agency)* declared that, with the exception of fluoxetine, all SSRI antidepressants had not shown efficacy in pediatric patients with depression and that they did pose a risk of presenting suicidal ideas or behaviour.

The FDA asked manufacturers to include in their labelling a warning statement in the patient information sheet that recommends close observation of children and adults under treatment given the possible increase in risk. Finally in October 2004, following the recommendations by the group of experts from the FDA´s *Psychopharmacologic*

Drugs Advisory Committee and the *Pediatric Drugs Advisory Committee* this warning was made compulsory. The warning informed that the current evidence showed that an increase in suicidal risk was quite possible in children and adolescents under treatment with these drugs. It is therefore recommended an adequate evaluation of the risk benefit relationship and close monitoring of the patient.

The *"black box warning"* refers to the most serious warning that can be found in the product labelling. It does not allow for publicity of the product addressed to health professionals with regard to this indication. Besides the warning, an information sheet is offered for the patient with every prescription. This sheet makes reference to the risks and precautions that should be taken while under treatment. This practice was extended to all antidepressants, after the acknowledgment that there was insufficient evidence at the moment to exclude any of the drugs. A reminder was also made that fluoxetine was the only approved treatment for depression in children and adolescents. There was no intention of prohibiting the prescription of these drugs, rather this information served as a forewarning to clinicians to take into account the risks involved and to balance the risk-benefit relationship when making management decisions. A recognition was made of the severe consequences of major depression and other psychiatric disorders that were not treated adequately.

The recommendations were based on the results of a meta-analysis[20] of 24 randomized, placebo-controlled trials in children and adolescents. It was concluded that the risk (odds ratio, OR) of presenting suicidal thoughts or behaviour was twice in the case of the group under treatment with antidepressants compared to the placebo group (4% vs 2%). A summary of the study can be found in table 1.

Suicide risk appears to increase in the first weeks of treatment with antidepressants, especially in children and adolescents

CONTENTS OF THE "BLACK BOX WARNING" (FDA, 2004)
SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behaviour (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients. Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of [nine] anti-depressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive –compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behaviour (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

In May 2007 the FDA decided to extend these warnings to patients between 18 and 24 years of age. This was based on the results of another meta-analysis including 372 randomized, controlled clinical trials on antidepressants in patients with major depression and other disorders[21] (table 2). Petitioned by the FDA, the pharmaceutical industry revealed data on adult patients under treatment with these drugs, for depression or other motives. Some of these results were suspisciously not published before[22].

Psycotherapy is still the elective management option in cases of mild and moderate depression, both in children and in adults

The data in children were the same from the 2004 study. In the overall analysis there was no increase in risk. However, when stratifying according to age, the supposedly protective effect of antidepressants against suicide demonstrated in patients over 65 years was reduced with decreasing age. Therefore, this could mean that there is a risk for children, adolescents and young adults, although in the latter no statistical significance was reached. In adults between 24 and 65 years the effect was apparently neutral. According to this study the effect of the antidepressants on suicidal thoughts and behaviour were age dependent. The risk was reduced and benefits increased with age.

EXTENSION OF THE "BLACK BOX WARNING" (FDA, 2007)
SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with anti depressants compared to placebo in adults beyond age 24; there was a reduction in risk with anti-depressants compared to placebo in adults aged 65 and older. *Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide.* Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

It cannot be ruled out that the use of antidepressants increases the risk of suicide in juveniles. Although statistical significance was not reached, the suspiscion of possible risk was sufficient to convince the panel of experts to extend the warning to patients under 24 years of age. Paradoxically, in 2009 the FDA approved the use of escitalopram for the treatment of major depressive disorder in adolescents between 17 and 24 years of age.

Another complication: publication bias

As mentioned before, the systematic review of the studies on antidepressants in children brought to light a preoccupying phenomenon: not all the studies carried out are finally published. This type of bias is frequent in the study of interventions within the health field. The pharmaceutical industry has proved to be a considerable influence in clinical trials and not always in the positive sense. At the same time, studies with negative results also turn out to have more difficulties in getting published.

The case of antidepressants is one of the most significant in medical literature, especially in studies on efficacy and safety. Cases have been shown where results were not published due to negative or dubious results[23,24]. For instance in the case of paroxetine in Major Depressive Disorder in children, some studies carried out by the pharmaceutical industry were not published[25]. Not only did these studies not show efficacy, they did suggest that there was a possible increase in the risk for suicide within this age group. A meta-analysis comparing the published trials with those unpublished showed that the inclusion of the unpublished data changed the orientation of the conclusions with an unfavourable risk-benefit relationship for all SSRIs except for fluoxetine[26].

What happened in Spain?

In June 2004, the Spanish Medicines Agency (Agencia Española de Medicamentos y Productos Sanitarios) issued an alert stating that the existing evidence did not support the use of SSRIs and related drugs for the management of depression in children and adolescents. The agency did however support the hypothesis of an increase in the risk of self injury. In December of the same year, an update of the information was issued, pointing out that consideration was being made to approve the use of fluoxetine for depression within these age groups, given that it was the only drug that had shown moderate efficacy in two clinical trials when compared to placebo. Currently fluoxetine remains the only antidepressant indicated in children and adolescents, in those cases where psychotherapy has not been effective.

Table 1. Meta-analysis by *Hammad et al* that led to the first *"black box warning"*.

TYPE OF STUDY	FINDINGS	STRENGTHS	LIMITATIONS
Meta-analysis Sample: children and adolescents	The risk (OR) of presenting suicidal thoughts or behaviour in the group treated with SSRI was twice that found in the placebo group (4% vs 2%)	Meta-analysis of 24 randomised, double-blind, placebo-controlled trials	These are studies designed to evaluate the response to drugs, not the risk of suicide. Patients at high risk for self injury at that time or a history of severe self harming events were excluded. There were no cases of suicide in any of the groups. Randomization cannot be assured (there were fewer severe patients assigned to the placebo group) A series of post-hoc analyses carried out increases the possibility of finding positive results at random. Differences in the design of individual studies. Differences in the concept of "suicide risk." Short follow-up period (4-6 weeks)

What evidence do other studies offer?

The comparison of different classes of antidepressants (mainly SSRIs and tricyclic drugs) and their relation to suicide has also been studied in observational studies. The lack of randomization in these trials confers these studies less evidence than clinical trials, with the tendency that the more severe patients are more frequently treated with SSRIs. Nevertheless, they do have advantages including longer observation periods, larger samples and more realistic conditions of treatment. In general there is an increased risk of suicidal thoughts and behaviour in the first few weeks of treatment and the SSRI class does not increase that risk more than any other antidepressants do[27].

Taking into account ecological studies, the majority of the countries show a positive correlation between the prescription of antidepressants and a reduction in the rates of suicide[28,29], although these studies do not establish causal relations. However, given the marked vulnerability for confounding factors, these results require confirmation through well designed controlled trials (table 3).

Unforeseen consequences

The warnings issued had the aim of alerting clinicans to closely monitor those patients taking antidepressants in the first few months of treatment. However, some later studies showed that there was no increase (or a very slight increase) in the number of follow-up consultancies[30,31]. Even more so, other unexpected consequences were observed:

· A reduction in the diagnosis of new cases of depression in both children[32,33,34] and adults.

· A reduction in the prescription of antidepressants in children[35].

· An increase in the rates of suicides in young patients[36] after years during which the incidence was decreasing[37].

Table 2. Meta-analysis by *Stone and cols* that led to the extension of the *"black box warning"* to patients under 24 years.

TYPE OF STUDY	FINDINGS	STRENGTHS	LIMITATIONS
Meta-analysis of 372 trials on antidepressants in patients with major depression and other psychiatric disorders. Sample: all age groups (data from the Hammad study; data from studies in adults carried out by the pharmaceutical industry and released for the FDA)	**Overall analysis:** no increase in risk **Stratification by age:** Over 65 years: protective effect of antidepressants, HR = 0.39 (0.18 - 0.78) Adults between 31-65 years: HR = 0.77 (0.60 - 1.00) Adults between 24- 30 years: HR = 1.00 (0.61 - 1.69) Adults between 18 - 24 years: HR = 1.55 (0.91 - 2.70) Children: HR = 2.22 (1.40 - 3.60)	Randomized double-blind, placebo-controlled trials	Studies designed to evaluate response to drugs not suicide risk. Patients with active suicide risk or past severe events were excluded. Patients with no mental health problems were excluded (lower incidence of suicide). Few cases of suicides (some trials with no cases). Randomization not assured (fewer severe patients in the placebo group). Treatment efficacy not shown. Placebo group: more difficult detection of suicide attempts (asymptomatic) and associated to placebo overdose. Studies do not represent the general population (results cannot be applied to general population) Short follow-up periods (8 weeks).

Table 3. Conclusions from other studies on the relationship between antidepressants and suicide.

TYPE OF STUDY	FINDINGS	STRENGTHS	LIMITATIONS
Observational studies	Increase in suicide risk in first few weeks but SSRIs = tricyclics	Long observation periods More realistic study conditions	Few cases of suicide (less statistical power) Indication bias (severe cases: SSRIs)
Ecological studies	Evidence suggests suicide rates decrease with the increased prescription of antidepressants.	Can detect small aggregate effects in large exposed populations Long periods of observation	Vulnerability for confounding factors (Advantage: can generate hypotheses from them)

DIAGNOSIS OF DEPRESSION
SYMPTOM DIFFERENCES OF DEPRESSION IN CHILDREN AND ADOLESCENTS WHEN COMPARED TO ADULTS

1. Lower capacity for verbal expression of sentiments.
2. In smaller children, somatic symptoms or complaints of "not feeling well" may be present that require a differential diagnosis with physical illness. Other forms of presentation at this age include anxiety as a result of a separation, phobias and alterations in behaviour.
3. In adolescents the main symptoms are irritability, restlessness, substance use and school related problems.
4. Higher frequency of atypical symptoms (emotional reactivity, weight increase or slow psychomotor functioning).
5. Prevalence of endogeneity increases with age.
6. More difficult diagnosis of maniac phases (predominance of irritability over euphoria, rapid cyclations, mixed episodes).
7. Greater comorbidity with other disorders with overlapping symptoms (attention deficit disorder, anxiety disorders, dissocial disorders).

Source: Tratado de psiquiatría de la infancia y la adolescencia. Wiener Dulcan. Ed. Masson, 2006

In 2008 the FDA included an alert on the possible increase in the risk of suicidal ideas and behaviour in the product labelling of 23 drugs used for the treatment of epilepsy, with no criteria for a *"black box warning"*. It seemed that this was a response to a petition by specialists in this field who feared that this could dissuade patients from starting or continuing treatment with antiepileptic agents.

An unresolved controversy

The evidence in favour or against the possible relation between antidepressants and suicide available up to now is not clear and the controversy continues. The nature of the object under study, suicide, complicates the possibilities of resolving the problem. It has been demonstrated that there is a confluence of varying factors (social, cultural, psychopathological and biological), with different definitions, and conceptual classifications. On the other hand, it does represent the natural unfolding of an affective disorder and can occur in combination with other disorders such as substance abuse, schizophrenia or personality disorders.

Although it has not yet been demonstrated that antidepressants have a direct effect on the prevention of suicide, this benefit is taken for granted. This is based on its efficacy in treating episodes of depression, and therefore, the reduction of the risk of self injury associated, especially in cases of major depression[24]. Some authors, based on their studies, defend the use of different SSRI agents specifically for suicidal ideation, regardless of the antidepressive effects (Perdersen, Banerjeen, Cooper, Finnegan and Ridle, among others). In a review of the evidence on the relation between antidepressants and suicide treatment, it was concluded that suicidal ideation is one of the three symptoms that improve with the use of SSRIs[38]. With regard to the estimated risk of untreated depression, the risk of suicide in the lifetime of a patient with depression is between 2.2 and 15%[39].

The widespread use of antidepressants for different disorders other than severe depression is a matter of concern as the risk-benefit relation is not as favourable

On the other hand, it seems that in some patients, starting treatment could bear an increase in risk. The most probable mechanisms by which antidepressants could induce suicidal ideation or behaviour in a small proportion of depressed patients, mainly juveniles, are the following:

· Clinical improvement in the first few weeks of treament, especially psychomotor inhibition permits patients with suicidal thoughts to either consummate them or simply verbalize them[40,41].

· Induced by the akathisia[42,43] and other secondary effects, such as insomnia, associated with these drugs[44]. The relation between antidepressants and suicide could be considered in this case as phenomenon similar to the more serious adverse effects.

· The possibility of underdiagnosis of cases of bipolar disorder among the cases of depression. This disorder implies a higher suicide risk and a weaker response to antidepressants[45,46]. Some of the factors that may contribute to these diagnostic errors include: greater prevalence of depressive symptoms compared to mania in the initial stages of the bipolar disorder, maniac symptoms are more likely to occur unnoticed than depressive symptoms, and the presentation of mixed episo-

des. Inadequate management can complicate the diagnosis and worsen the prognosis.

· The comorbidity of other disorders that may by themselves pose a risk of suicide, for instance personality disorders and impulse control disorders[47].

· Undetected cases of patients resistant to treatment, where any worsening of the episode may induce self injurious ideation resulting from desperation.

It seems logical that this controversy on the use of antidepressants should have resulted in a more controlled use of these drugs. However, during all these years, we have witnessed an increase in their prescription, not only in cases of major depression, but in other disorders of lower suicidal risk, such as anxiety or mild depressive episodes where the risk-benefit relation is not as favourable[48]. The risk associated with their use, which apparently affects especially children and adolescents has led experts to recommend psychotherapy as the first management option in mild and moderate depression.

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Conclusions

It cannot be ruled out that the use of antidepressants increases the risk of suicide in some age groups, like juveniles, or in cases of low suicidal risk.

There are no randomized controlled trials that resolve this controversy.

It is essential to carry out well designed trials to specifically clarify this question.

Antidepressants are recommended only for the approved indications. Close patient supervision must be ensured to provide early detection of complications.

Psychotherapy remains the elective management option in cases of mild and moderate depression both in children and in adults.

NICE recommendations. Children and adolescents.

SEVERITY	ELECTIVE OPTION	ALTERNATIVE		
Mild depression	Psychotherapy[1] for 2-3 months	If no response, refer to moderate/major depression guideline		
Moderate/severe depression	Psychotherapy for at least 3 months	Psychotherapy combined with antidepressants[2]	If psychotic symptoms are present consider adding antipsychotic agents[3]	If high risk consider admission[4]

1. Psychotherapy: individual cognitive behavioural therapy, interpersonal therapy or short-term family therapy

2. Antidepressants:
· Require prescription by child psychiatrist.
· Always given in combination with psychotherapy.
· Good clear information should be provided to the family, who should sign a fully informed consent form. The patient should be monitored closely (weekly contacts for at least the first 4 weeks).
· Fluoxetine is the only antidepressant that has shown evidence in clinical trials where the benefits outweigh risks. When treating children between 5 and 11 years then precaution is necessary as the efficacy has not been shown in this age group.
· Treatment starts with 10 mg and if needed can be increased to 20 mg after a week if clinically necessary.
· If not well tolerated due to secondary effects, then another antidepressant can be considered. Sertraline and citalopram (not recommended by the EMA) are recommended as alternative treatments. The dose is usually half that employed in adults. If clinically necessary increments can be made up to the adult dose in the following two to four weeks.
· Paroxetine, venlaxafin and tricyclic antidepressants should not be employed in the management of depression in children and adolescents.
· If there is a favourable response, treatment should be maintained for at least 6 weeks after the remission of the disorder (remission defined as absence of symptoms and full functioning of the individual for at least 8 weeks).

3. In case of major depression with psychotic symptoms, then atypical antipsychotic agents can be considered. Duration of treatment and adequate doses have not been established.

4. In cases of high suicidal risk or self harm, high risk of self neglect, or refusal to take medication, then admission for specialized care should be considered.

NICE recommendations. Adults.

SEVERITY	ELECTIVE OPTION	ALTERNATIVE		
Mild or subclinic depression	Psychotherapy[1]	Add antidepressant[2] if: · No response to other interventions. · History of a moderate/severe episode. · Worsening of previous long term subclinical symptoms (two years).		
Moderate/major depression	Intensive psychotherapy combined with antidepressant	· Increase dose if inadequate response. · Augmentation: lithium, antipsychotic drugs, other antidepressants.	If no response consider ECT[3]	If risk consider admission

1. Psychotherapy: Cognitive-Behavioural Therapy

2. Antidepressant Treatment:
· Commence with a SSRI: given the same degree of efficacy among the different SSRI agents, the choice of drug should be based on the expected profile of side effects or on the previous experience of the patient with these agents.
· Inform the patient on: gradual effect of the antidepressant, need for treatment, possible side effects and interactions.
· Intensify follow up in patients at risk of suicide or under 30 years old (where there is a risk of self harm or suicide in the first few weeks).
· If there is no response in 3-4 weeks, consider increasing the dose or changing the drug in cases of secondary effects or preference of the patient.
· If there is a favourable response, then treatment should be maintained for at least 6 months after the remission of symptoms (defined as the absence of symptoms and full functioning for at least 8 weeks). Psychotherapy can be employed as a complement to prevent relapses in high risk patients.

3. ECT: Electroconvulsive therapy.

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