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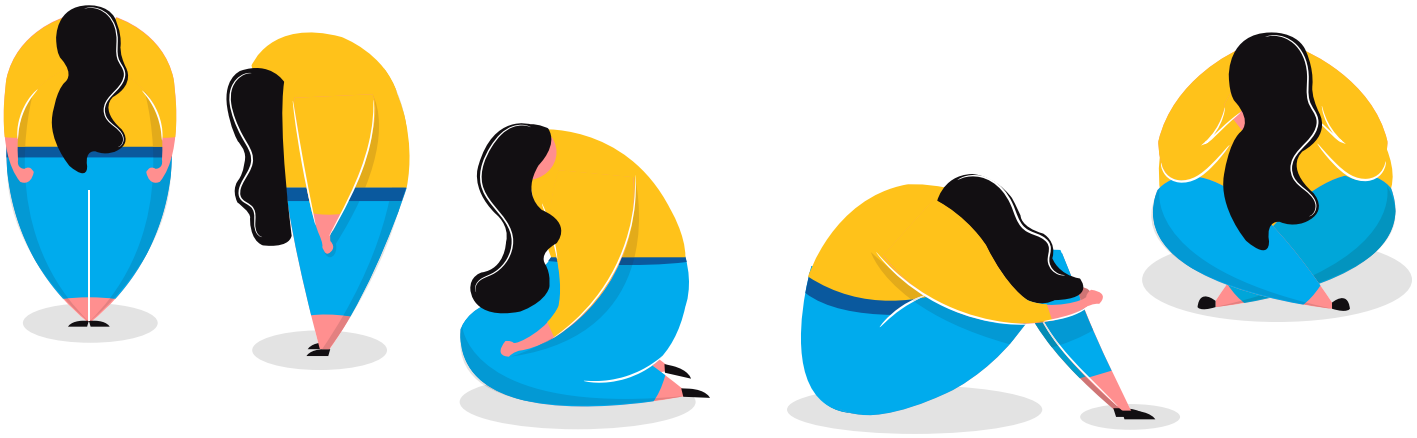
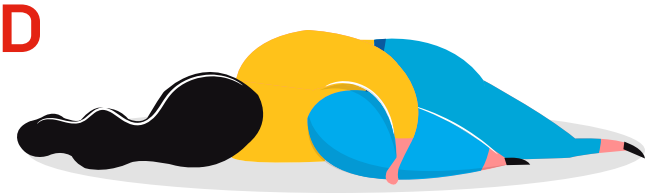


SUICIDALITY ASSOCIATED WITH THE USE OF ANTIDREPRESSANTS IN CHILDREN AND ADOLESCENTS



INTRODUCTION Suicide is a public health problem in the infant and adolescent population and is one of the leading causes of death in that age range. Since the introduction of new classes of antidepressants in the early 1990s, concerns about the risk of suicidality associated with the use of these drugs in children and adolescents began to appear. Since then, numerous studies have been published in this regard, and several regulatory agencies have issued warnings concerning this possible increased risk. Despite this, the use of antidepressants in this population continues to increase. OBJECTIVE To analyse the evidence for the relationship between antidepressant use in children and adolescents and the risk of suicidality. In addition, to determine the relationship between this use and the onset of serious adverse events, as well as the treatment discontinuation due to such events. METHODS A literature search was carried out in MedLine and the Cochrane Library. Reviews were prioritised and, if necessary, the search was broadened to include randomised clinical trials. Studies concerning treatment with any antidepressant, irrespective of the diagnosis, compared with placebo, any non-pharmacological treatment or no treatment were analysed. Additionally, position papers from scientific societies and healthcare institutions were also identified. The prescriptions database of the Navarre Health Service was used to obtained information regarding antidepressant use in children and adolescents in Navarre, and the BIFAP (www.bifap.org) database was used to obtain this information for Navarre and Spain as a whole. CONCLUSIONS Current evidence indicates that antidepressants increase the risk of suicidality in children and adolescents. Therefore the use in this population should be restricted and they should only be used for the authorised indications. This risk is closely related to an increase in suicidal ideation. Indirect evidence suggests that the risk of suicidality may be higher with venlafaxine. There is insufficient evidence that any antidepressant reduces this risk. There is a large body of evidence that antidepressants increase the risk of serious adverse events and discontinuations due to adverse events under any indication in comparison with placebo. In the studies available, the safety is analysed when treatment starts and, in general, these are short-term studies, therefore the risk of this type of adverse event in the long term cannot be ruled out.

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MARTA GUTIÉRREZ | LEIRE LEACHE | LUIS CARLOS SAIZ
Unit of Innovation and Organization. Navarre Health Service, Pamplona, Spain

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Introduction

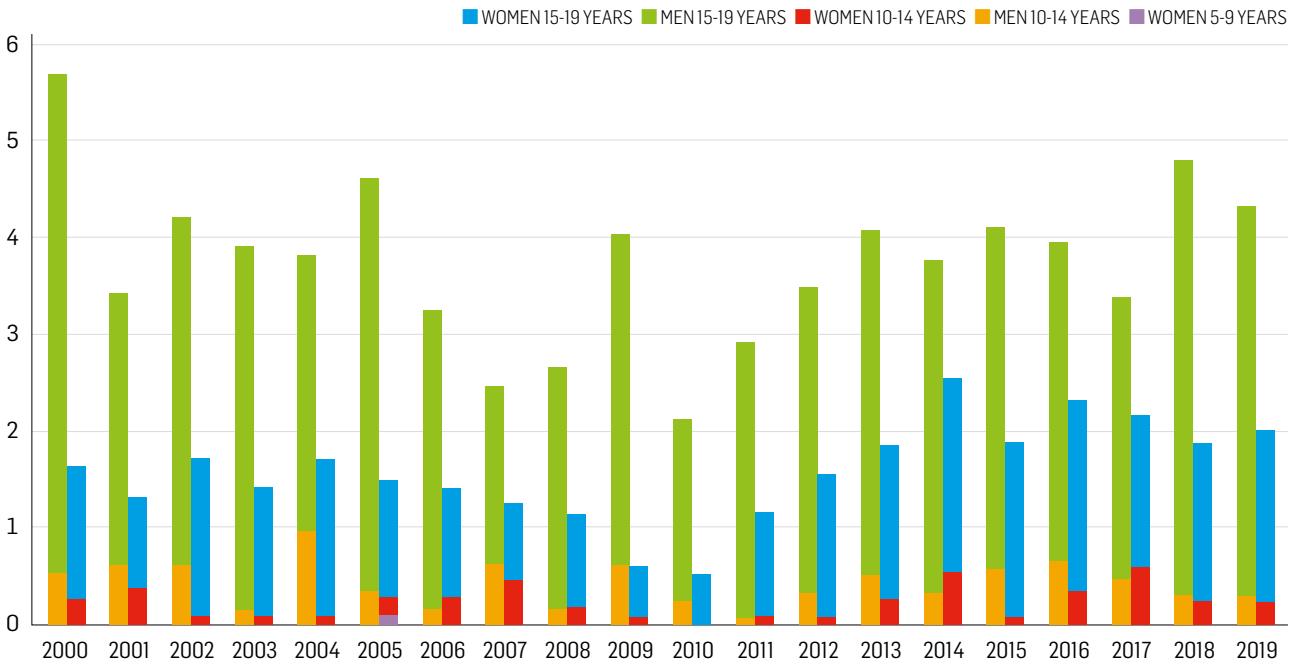
According to the results of the National Health Survey 2017, the prevalence of disorders such as depression or anxiety in the infant population (0-14 years) in Spain is 0.6%[1]. Moreover, depression is an important risk factor for suicide in adolescents[2]. According to data from 2013, suicide was the third leading cause of death in Spain in people aged 15-29 years and was higher in men than in women[3]. Figure 1 shows the evolution in people aged less than 20 years in Spain[1].

Antidepressant use in children and adolescents has been associated with an increase in suicidality. The first warning signs were detected in 1990[4], and the worry began to be more widespread in the early years of this century[5]. Since then, suicidality associated with antidepressant use in children and adolescents have been the focus of numerous studies, and several regulatory agencies and organisations have published reviews in this regard[6–8], the results of which have led the Food and Drug Administration (FDA) and other regulatory agencies to issue notices warning of the risk of antidepressant use in this population. The Spanish Medicines Agency also issued several warnings in this regard in 2004 and 2005[9–11].

The ability to obtain clear and detailed evidence in this regard tends to be hindered by aspects such as the low incidence of this type of adverse event, and subsequent lack of statistical power, publication bias in the safety findings (including the non-publication of studies and selective publication of results), the limited transparency as regards access to individual data from clinical trials with drugs or the publication of biased data or analyses by pharmaceutical companies[5,12,13].

Despite the warnings and significant suspicions of an increased risk of serious adverse events, especially those related to suicidality, antidepressant use in children and adolescents continues to increase[14–17].

Figure 1. Deaths due to suicide and self-harm in people aged less than 20 years per 100,000 inhabitants for the corresponding age group and sex in Spain (2000-2019). Source: INE[1].



Antidepressant use in Navarre and Spain

According to data from 2020, in Navarre a total of 5209 young people aged between 0 and 17 years used psychotropic drugs (4.3% of this population), of which 9.8% (513) were taking antidepressants (Figure 2). This means that 0.4% of the population in this age range received antidepressant treatment.

Figure 3 shows the evolution of the prevalence of antidepressant use in the population aged 0-17 years in Navarre and for those Spanish Autonomous Communities participating in the Primary Care Pharmacoepidemiological Research Database (BIFAP)[18].

With respect to the type of antidepressant used, sertraline was the most widely used antidepressant in this population in 2020 (52%), followed by fluoxetine (20%), trazodone (11.4%) and escitalopram (9.1%).

Objective

The aim of this publication is to analyse the evidence for the relationship between antidepressant use in children and adolescents and the risk of suicidality. As used here, the term "suicidality" includes attempts to self-harm, suicide, suicidal ideation and suicidal behaviour.

In addition, the relationship between this use and the onset of serious adverse events, as well as treatment discontinuation due to adverse events, will also be studied.

Figure 2. Population of Navarre aged 0-17 years using psychotropic drugs (year 2020) by sex. Source: Sub-Directorate for Drugs and Care. Navarre Health Service, Pamplona, Spain.

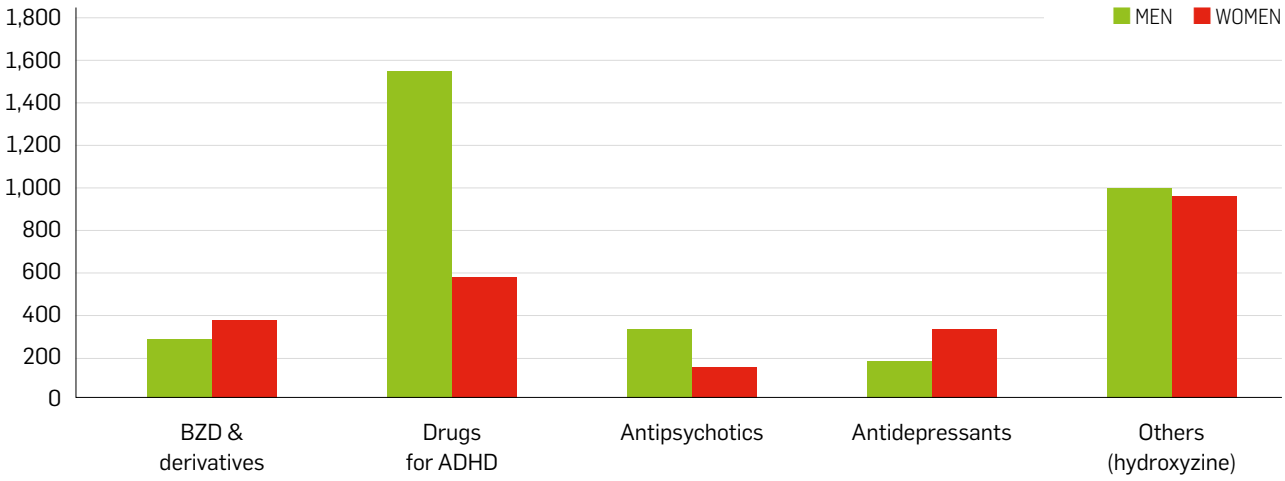
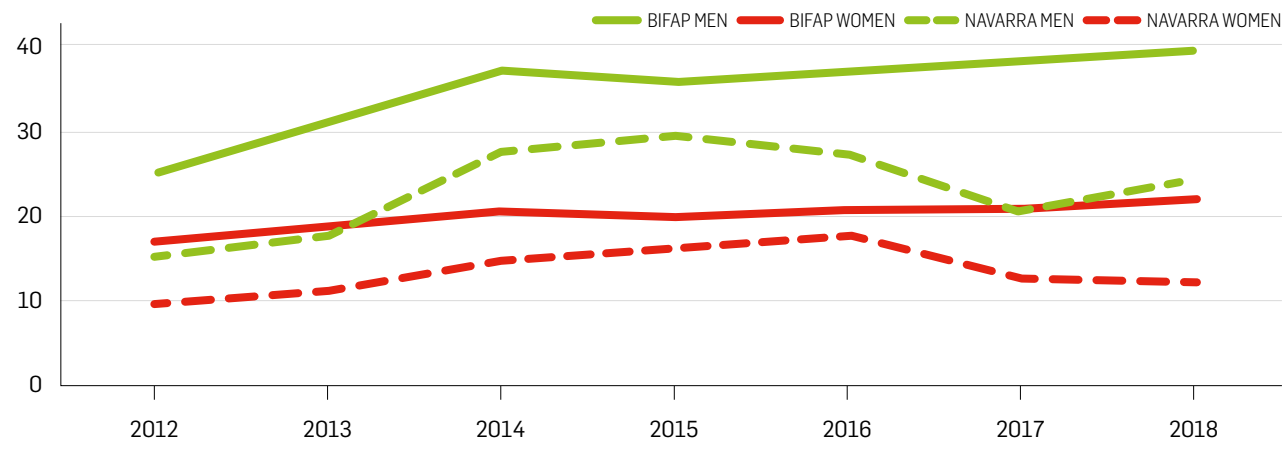


Figure 3. Prevalence of antidepressant use in the population aged 0-17 years in Navarre and in the rest of Spain[18] (number of patients in treatment for at least one day in each year per 10,000 persons. All drugs with ATC N06A are included, except duloxetine and clomipramine, which are not currently available in BIFAP).



Criteria for study selection and search strategy

Studies concerning treatment with any antidepressant, irrespective of the diagnosis, compared with placebo treatment, no treatment or any non-pharmacological treatment were analysed. A literature search was carried out in *MedLine* and *The Cochrane Library* in November 2020. Reviews were prioritised and, if necessary, the search was broadened to include individual randomised clinical trials (RCTs). Additionally, position papers from scientific societies and healthcare institutions were also identified.

Review of the evidence available

A summary of the results presented below can be found in Appendix A.

Suicidality

In 2003 the FDA commissioned the drafting of an independent external report that included published and unpublished information from clinical trials regarding antidepressant-related adverse events in children and adolescents. The evaluation of 23 RCTs showed that antidepressants increased suicidality by 78% in comparison with placebo (relative risk (RR) 1,78; 95%CI 1.14-2.77)[19]. In light of these findings, the FDA issued a black box warning in October 2004 (updated in 2006), warning that "antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders"[20].

In 2005, the EMA Committee for Medicinal Products for Human Use reviewed the information from clinical trials submitted by companies to the regulatory agencies, and the data from scientific publications and observational studies, to analyse the risk of suicidality related to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) in children and adolescents. They concluded that suicidal behaviour (suicide attempts and suicidal thoughts) and hostility (mainly aggression, confrontational behaviour and anger) were more common amongst children taking antidepressants than their counterparts taking placebo in the studies identified[8].

A Cochrane review published by Hetrick et al. in 2012 compared the use of SSRI-type antidepressants, SNRIs, reboxetine, bupropion, agomelatine and mirtazapine with placebo in children and adolescents with depressive disorder[21]. It was found that antidepressants were associated with a greater risk of suicide-related events than placebo (OR 1.58, 95%CI 1.02-2.45; 17 studies; n=3229; low quality of evidence). In 2021 the same author published a new review concerning children and adolescents with major depressive disorder in which the effect of different types of antidepressants was analysed separately[22]. Statistically significant differences were only found for venlafaxine, which showed an increase in suicide-related events: OR 13.84, 95%CI (1.79-106.90) (low quality of evidence). Paroxetine was also associated with an increased risk after removing studies with a high risk of bias from the analysis: OR 2.55, 95%CI (1.08-6.02).

Despite the warnings from regulatory agencies, antidepressant use in children and adolescents continues to increase

"Suicidality" includes attempts to self-harm, suicide, suicidal ideation and suicidal behaviour

A systematic review and meta-analysis regarding the safety of antidepressants was published in 2016 using the data from clinical study reports (CSRs)[12]. CSRs are documents concerning individual clinical trials prepared by the sponsors that include detailed information about each trial. These documents are used by the regulatory agencies to establish the drugs marketing authorisation proposal. This review included information from 70 double-blind RCTs, involving a total of 18,526 participants, involving different SSRIs and SNRIs. Eleven of the included studies were carried out in 2184 children and adolescents, thus representing 12% of all patients. No suicide or death was reported in trials with children or adolescents. The risk of suicidality was found to be significantly higher in children and adolescents receiving antidepressants compared with those receiving placebo (OR 2.39; 95%CI 1.31-4.33).

A meta-review published by Boaden et al. in 2020, which included systematic reviews and meta-analyses concerning the safety and efficacy of antidepressants in chil-

dren and adolescents for a wide range of indications, was identified[23]. The majority of the systematic reviews and meta-analyses included were considered to be of high or moderate quality. One of the reviews included, which was published by Dobson et al.[24], obtained unfavourable results for tricyclic antidepressants in comparison with placebo, but no differences with respect to SSRIs or SNRIs. This review was considered to be of critically low quality. Another of the reviews included, which concerned autism spectrum disorders and published by Williams et al. in 2013, did not find any significant differences between fluoxetine and the control group on the suicide sub-scale of the Overt Aggression Scale (OAS). A network meta-analysis published in 2016 also included in the meta-review, which analysed the risk of suicidal behaviour and ideation with the use of antidepressants of any kind in children and adolescents with depressive disorder, found that venlafaxine was associated with a higher risk in comparison with placebo (estimated OR 7.7; 2 RCTs; n=367), with no differences being found between placebo and the remaining antidepressants[26].

A review and network meta-analysis published by Zhou et al. in 2020 compared the safety and efficacy of antidepressants and psychotherapy for the treatment of depressive disorder in children and adolescents[27]. This review included 37 trials with published and unpublished data that compared antidepressants of any type versus placebo. These authors found a statistically significant increase in the risk of suicidality (suicidal ideation and behaviour) with venlafaxine when compared with placebo (OR 8.31; 95% credibility interval (95%CrI) 1.92-343.17), although with a low quality of evidence. This higher risk associated with venlafaxine was maintained upon comparison with cognitive behavioural therapy (CBT) and family therapy (FT) (CBT vs. venlafaxine: OR 0.10; 95%CrI 0.00-0.50; FT vs. venlafaxine: OR 0.12; 95%CrI 0.00-0.78), whereas no statistically significant differences were found for other drugs.

> The evidence available shows that antidepressants are associated with a higher risk for the onset of suicidality.

Suicide attempts

The review by Sharma et al. based on CSRs concerning all suicide attempts in children and adolescents, including intentional self-harm, intentional overdose and preparatory events, did not find statistically significant differences when comparing SSRIs or SNRIs with placebo, although important differences cannot be ruled out based on their confidence intervals (OR 1.85; 95%CI 0.90-3.83)[12]. A review published in 2009, which included five observational studies with a total of more than 60,000 patients aged between 6 and 19 years with moderate to severe depression, found that the risk of suicide or attempted suicide was higher in patients treated with SSRIs compared with no antidepressant treatment (OR 1.92 95%CI 1.51-2.44)[28].

Antidepressants are associated with an increased risk of suicidality

The combined evidence from clinical trials and observational studies suggests an increased risk of attempts to self-harm with antidepressants

> No statistically significant differences in terms of the risk of suicide attempts have been found in clinical trials when comparing the use of SSRIs or SNRIs with placebo due to the low number of cases. However, the evidence from clinical trials and observational studies does tend to suggest an increased risk.

Suicidal ideation

The review by Sharma et al., in which the data concerning suicidal ideation events in children and adolescents were obtained from the narratives and lists of adverse events for individual patients recorded in the CSRs, concluded that the risk of suicidal ideation was significantly higher with the use of SSRIs or SNRIs than with placebo (OR 3.29 95%CI 1.25-8.62; 11 studies; 1797 patients)[12].

> The risk of suicidal ideation is more than threefold higher with SSRIs or SNRIs in comparison with placebo.

Suicide

No case of suicide was found amongst the participants in any of the two treatment arms (antidepressant or placebo) in the reviews by the FDA[19], Sharma et al.[12], Bridge et al.[29], Ipser et al.[30] or Hetrick et al.[21].

In the review of observational studies cited above, the risk of completed suicide was fivefold higher with SSRIs (OR 5.81 95%CI 1.57-21.51)[28].

> According to observational evidence, SSRIs significantly increase the risk of suicide compared with not using them.

Treatment discontinuation due to adverse events

The review by Locher et al. published in 2017, which included studies carried out in children and adolescents with depressive disorder, anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder, found that the risk of discontinuation due to adverse events was 79% higher in subjects treated with SSRIs/SNRIs than with placebo (RR 1.79 95%CI 1.38-2.32)[31].

The meta-review by Boaden et al. discussed above provides data concerning discontinuations due to adverse events depending on the indication for the drugs in different systematic reviews[23]. For anxiety disorders, one review found an increased risk with SSRIs but not with SNRIs or tricyclic antidepressants[24]. In addition, no statistically significant differences were found when studying each drug individually. Another review of anxiety disorders found an increased risk for antidepressants in general (RR 1.91 95%CI 1.20-3.05), and for sertraline and fluoxetine in particular[30]. For depressive disorder, the review by Cipriani et al. found a higher discontinuation with imipramine (OR 5.49 95%CI 1.96-20.86), venlafaxine (OR 3.19 95%CI 1.01-18.70) and duloxetine (OR 2.8 95%CI 1.20-9.42) but not with the other antidepressants studied[26].

In the review and network meta-analysis published by Zhou et al., of the 37 trials comparing antidepressants with placebo in children and adolescents, a statistically significant increase in discontinuations due to any cause was only found when comparing imipramine with placebo (OR 2.51 95%CI 1.26-6.24)[27]. The quality of the evidence for this comparison was classified as moderate, but low or very low for the other comparisons.

> The evidence from clinical trials shows that, in general, antidepressants are associated with discontinuations due to adverse events.

Serious adverse events

The systematic review by Locher et al. published in 2017 analysed the risk of serious adverse events with the use of SSRIs and SNRIs in children and adolescents[31]. This review identified 36 RCTs, with 6778 participants, 51.4% of whom were female, with a mean age of 12.9 (SD 5.1) years. A higher risk of serious adverse events was fond with SSRIs (RR 1.71 95%CI 1.22-2.40; calculated NNH 41, 95%CI 21-133), SNRIs (RR 2.10 95%CI 1.19-3.69; calculated NNH 42 95%CI 17-243), and with either of the two pharmacological groups (RR 1.76 95%CI 1.34-2.32) when compared with placebo.

The risk of suicidal ideation is more than threefold higher with SSRIs or SNRIs in comparison with placebo

SSRIs significantly increase the risk of suicide according to observational evidence

SSRIs and SNRIs are associated with an increased risk of serious adverse events

> The use of SSRIs and SNRIs is associated with a marked increase in the risk of serious adverse events.

Recommendations from healthcare institutions

The EMA does not recommend the use of SSRIs and SNRIs in children and adolescents other than for authorised indications. In the event that, depending on the patient's needs, their use is considered necessary, the patient should be monitored closely to detect the onset of suicidal behaviour, self-harm or hostility, especially at the start of treatment. Similarly, treatment should not be interrupted without consulting with the physician, due to the possible onset of withdrawal syndrome, and, if discontinuation is started, the dose should be reduced gradually over several weeks or months[8].

The NICE guidelines concerning depression in children and young people published in 2019 state the following:

"A child or young person prescribed an antidepressant should be closely monitored for the appearance of suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment, by the prescribing doctor and the healthcare professional delivering the psychological therapy. Unless it is felt that medication needs to be started

immediately, symptoms that might be subsequently interpreted as side effects should be monitored for 7 days before prescribing. Once medication is started the patient and their parents or carers should be informed that if there is any sign of new symptoms of these kinds, urgent contact should be made with the prescribing doctor"[32].

The guidelines also states the following: "do not offer antidepressant medication to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. If an antidepressant is to be prescribed this should only be following assessment and diagnosis by a child and adolescent psychiatrist"[32].

The American Academy of Child & Adolescent Psychiatry guideline for anxiety disorders in children and adolescents recommends that cognitive behavioural therapy (1B: recommendation with moderate quality of evidence) or SSRIs (1B) be offered individually, or preferably in combination (2C: suggestion with low quality of evidence), and suggests that SNRIs may be offered (2C) to patients aged 6 to 18 years with social anxiety, generalised anxiety, separation anxiety or panic disorder[33]. It concludes that the limited data available prevented evaluation of the adverse events related to suicidal behaviour or ideation on the basis of the reviews analysed in this report[24,31].

Fluoxetine is the only drug approved for the treatment of depressive disorder in children and adolescents. The summary of product characteristics states that this drug is only indicated in children older than 8 years of age and adolescents for moderate to severe depressive episodes if there is no response to psychological therapy after 4-6 sessions. Antidepressant treatment should only be offered to children or adolescents with moderate to severe depression in combination with concurrent psychological therapy. It also states that suicidal behaviour (suicide attempts and suicidal ideation) and hostility (mainly aggression, oppositional behaviour and anger) were observed more frequently during clinical trials with children and adolescents treated with antidepressants than in those treated with placebo. Fluoxetine should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe depressive episodes, and should not be used in other indications in this age group. However, if treatment is decided on the basis of clinical needs, careful monitoring of the patient for the appearance of suicidal symptoms is required[34]. Fluoxetine is also authorised for the treatment of obsessive-compulsive disorder and bulimia nervosa in adults, but not in the paediatric population.

The summary of product characteristics for sertraline states the following: Sertraline must not be used for the treatment of children and adolescents younger than 18 years, except in patients aged 6 to 17 years with obsessive-compulsive disorder. Suicidal behaviour (suicide attempts and suicidal ideation) and hostility (mainly aggression, oppositional behaviour and anger) were observed more frequently during clinical trials with children and adolescents treated with antidepressants than in those treated with placebo. However, if treatment is decided on the basis of clinical needs, careful monitoring of the patient for the appearance of suicidal symptoms is required[35].

Atomoxetine is indicated for the treatment of attention-deficit hyperactivity disorder (ADHD) in patients aged 6 years and older. However, it was initially developed as an antidepressant, and suicidal behaviours (suicide attempts and suicidal ideation) have also been reported

The EMA recommends not using SSRIs and SNRIs in children and adolescents other than for authorised indications

Fluoxetine is the only drug approved for the treatment of depressive disorder in children and adolescents

Sertraline is approved for the treatment of obsessive-compulsive disorder in patients aged 6 to 17 years

If treatment is decided, careful monitoring of the patient for the appearance of suicidality is required

in patients treated with atomoxetine, therefore the same warnings apply. The summary of product characteristics states that in ADHD patients treated with atomoxetine, the appearance or worsening of suicidal behaviour should be monitored carefully[36].

The other antidepressants are not authorised for use in children and adolescents due to a lack of evidence in that population or due to safety concerns, especially related to suicidality. Despite this, the use of antidepressants outside the authorised indications is common.

Conclusions

Suicide is one of the leading causes of death in the infant and adolescent population, and is therefore a significant public health problem in that population.

Current evidence indicates that antidepressants increase the risk of suicidality in children and adolescents. Therefore the use in this population should be restricted and they should only be used for the authorised indications. This risk is closely related to an increase in suicidal ideation. Indirect evidence suggests that the risk of suicidality may be higher with venlafaxine. However, there is insufficient evidence that any antidepressant reduces this risk.

There is a large body of evidence that antidepressants increase the risk of serious adverse events and discontinuations due to adverse events under any indication in comparison with placebo.

The small sample size in many of the studies analysed, and the low frequency of events, especially suicide and attempted self-harm, often results in a lack of statistical power to find the possible differences in some variables.

In the studies available, the safety is analysed when treatment starts and, in general, these are short-term studies (4-12 weeks), therefore the conclusions are only applicable to the initial period of antidepressant treatment. Although the long-term risk of antidepressant use is uncertain, the possible onset of adverse events cannot be ruled out.

The publication bias in the safety results (including the non-publication of studies and the selective publication of data), the low transparency as regards access to individual data from clinical trials with drugs or the publication of biased data or analyses by pharmaceutical companies limits our ability to obtain clear and detailed evidence regarding the safety of antidepressants in this population.

Appendix A. Summary of the evidence concerning suicide-related adverse events and serious adverse events with the use of antidepressants in children and adolescents.

OUTCOME VARIABLES	GLOBAL	DEPRESSIVE DISORDER	ANXIETY DISORDER	OTHER INDICATIONS
Suicides	No cases found			
Suicidality	Sharma 2016 (11 RCT, CSR): SSRI/SNRI OR 2.39 (95%CI 1.31-4.33) Bridge 2007 (27 RCT): SSRI/NEF/VEN/MIR: RR 1.7 (95%CI 1.1-2.7)	Hetrick 2012 (18 RCT): SSRI/SNRI/REB/BUP/AGO/MIR: OR 1.58 (95%CI 1.02-2.45) Bridge 2007 (15 RCT): SSRI/NEF/VEN/MIR: NS **By individual drug:** Zhou 2020 (37 RCT): Venlafaxine: OR 8.31 (95%CI 1.92-343.17) Other drugs[a]: NS Hetrick 2021: Venlafaxine: OR 13.84 (95%CI 1.79-106.90) Sensitivity analysis: Paroxetine: OR 2.55 (95%CI 1.08-6.02) Other drugs[b]: NS Cipriani 2016 (30 RCT): Venlafaxine: OR 0.13 (95%CI 0.0-0.55) (placebo vs. venlafaxine) Other drugs[c]: NS	Bridge 2007 (6 RCT): SSRI/NEF/VEN/MIR: NS Dobson 2019 (16 RCT): SSRI: Log OR −1.0 (95% CrI −4.7 to 2.2) SNRI: Log OR −0.6 (95% CrI −2.8 to 1.2) TA: Log OR −25.1 (95% CrI −57.4 to −4.5) **By individual drug:** Dobson 2019: Paroxetine: Log OR −20.0 (95% CrI −60.4 to −1.7) Sertraline: Log OR 19.8 (95% CrI 0.7-61.7) Other drugs[d]: NS	**OCD**: Bridge 2007 (6 RCT): SSRI/NEF/VEN/MIR: NS
Attempted self-harm	Sharma 2016 (11 RCT, CSR): SSRI/SNRI OR 1.85 (95%CI 0.90-3.83)	Bridge 2007 (15 RCT): SSRI/NEF/VEN/MIR: NS	Bridge 2007 (6 RCT): SSRI/NEF/VEN/MIR: NS	**OCD**: Bridge 2007 (6 RCT): SSRI/NEF/VEN/MIR: NS
Suicidal ideation	Sharma 2016 (11 RCT, CSR): SSRI/SNRI OR 3.29 (95%CI 1.25-8.62)	Bridge 2007 (15 RCT): SSRI/NEF/VEN/MIR: NS	Bridge 2007 (6 RCT): SSRI/NEF/VEN/MIR: NS	**OCD**: Bridge 2007 (6 RCT): SSRI/NEF/VEN/MIR: NS
Serious adverse events	Locher 2017 (36 RCT): SSRI/SNRI RR 1.76 (95%CI 1.34-2.32) SSRI: RR 1.71 (95%CI 1.22-2.40) SNRI: RR 2.10 (95%CI 1.19-3.69)	Locher 2017 (14 RCT): SSRI/SNRI RR 1.99 (95%CI 1.33-2.97) SSRI: RR 172 (95%CI 1.12-2.63) SNRI (3 RCT): RR 4.43 (95%CI 1.73-11.32)	Locher 2017 (6 RCT): SSRI/SNRI NS SSRI: NS SNRI: NS	**OCD**: Locher 2017 (2 RCT): SSRI: NS **PTSD**: Locher 2017 (1 RCT): **SSRI**: NS
Discontinuation due to adverse event (tolerability)	Locher 2017 (33 RCT): SSRI/SNRI RR 1.79 (95%CI 1.38-2.32) SSRI (27 RCT): RR 1.84 (95%CI 1.38-2.44) SNRI (6 RCT): RR 1.56 (95%CI 0.83-2.94)	Locher 2017 (17 RCT): SSRI/SNRI RR 1.66 (95%CI 1.20-2.28) SSRI: RR 1.40 (95%CI 0.99-1.98) SNRI: RR 2.95 (95%CI 1.65-5.40) **By individual drug:** Cipriani 2016 (30 RCT): Duloxetine: OR 2.8 (95%CI 1.20-9.42) Venlafaxine: OR 3.19 (95%CI 1.01-18.70) Imipramine: OR 5.49 (95%CI 1.96-20.86) Other drugs[e]: NS Zhou 2020 (37 RCT): *Discontinuation due to any cause:* Imipramine: OR 2.51 (95%CI 1.26-6.24) Other drugs[f]: NS	Dobson 2019 (16 RCT): SSRI: Log OR −1.8 (95% CrI −3.4 to −0.4) SNRI: Log OR 0.4 (95% CrI −0.9 to 1.7) TA: Log OR −0.8 (95% CrI −5.0 to 3.3) Individual drugs[h]: NS Locher 2017 (10 RCT): SSRI/SNRI RR 1.38 (95%CI 0.73-2.60) SSRI: RR 3.45 (95%CI 1.34-8.86) SNRI: RR 0.78 (95%CI 0.39-1.56) **By individual drug:** Ipser 2019 (20 RCT): All: RR 1.91 (95%CI 1.2-3.05) Sertraline: RR 2.60 (95%CI 3.14-10.25) Fluoxetine: RR 3.43 (95%CI 1.10-6.15) Other drugs[h]: NS	**ADHD**: Cortese 2018 (1 RCT): NS **PTSD**: Locher 2017 (1 RCT): **SSRI**: NS **OCD**: Locher 2017 (7 RCT): **SSRI**: RR 3.59 (95%CI 1.89-6.84)

a: CIT, CLO, DESV, DUL, ESC, FLU, IMIP, MIR, NEF, PAR, SER. **b:** FLU, SER, CIT, ESC, MIR, DESV, VIL, DUL, VOR. **c:** FLU, DUL, SER, CIT, ESC, PAR, IMIP, CLO. **d:** DUL, VEN, IMIP. **e:** FLU, DES, MIR, SER, CIT, ESC, PAR, NEF, AMI, CLO. **f:** NEF, VIL, NOR, FLU, MIR, DESV, CIT, DUL, VEN, AMI, PAR, ESC, SER, CLO, DES. **g:** FLUV, FLU, PAR, SER, DUL, VEN, CLO, IMIP. **h:** FLUV, PAR, CLO, VEN.

ADHD: attention-deficit hyperactivity disorder; AGO: agomelatine; AMI: amitriptyline; AT: tricyclic antidepressants; BUP: bupropion; CI: confidence interval; CIT: citalopram; CLO: clomipramine; CrI: credibility interval; DESV: desvenlafaxine; DUL: duloxetine; ESC: escitalopram; FLU: fluoxetine; FLUV: fluvoxamine; IMIP: imipramine; MIR: mirtazapine; NEF: nefazodone; NOR: nortriptyline; NS: not significant; OCT: obsessive-compulsive disorder; OR: odds ratio; PAR: paroxetine; PTSD: post-traumatic stress disorder; RCT: randomised clinical trial; REB: reboxetine; RR: relative risk; SER: sertraline; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VEN: venlafaxine; VIL: vilazodone; VOR: vortioxetine.

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